Medical Lib.

CHEMOTHERAPY NUMBER

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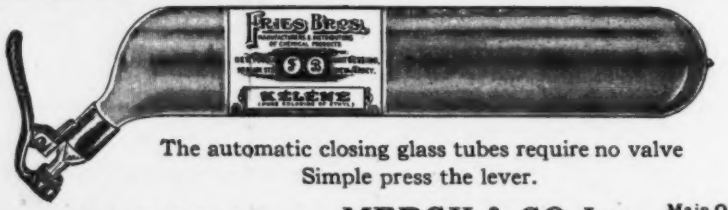

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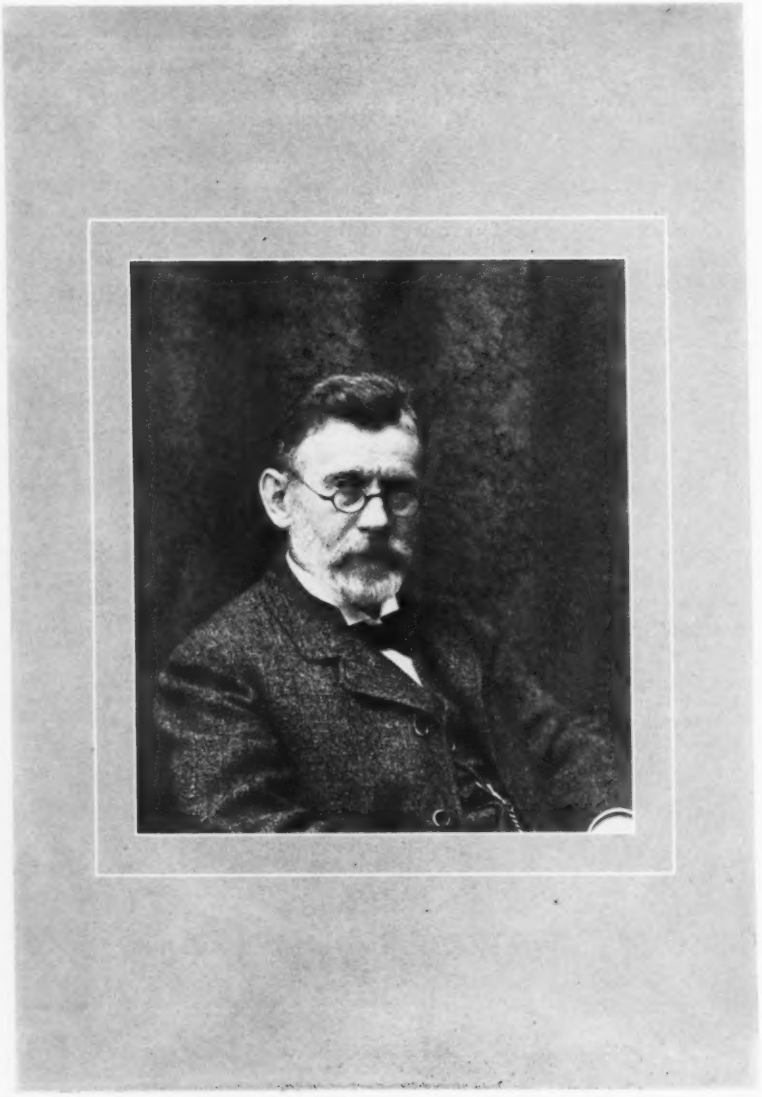

From Ehrlich's "Studies in Immunity".
John Wiley & Sons, New York, Publishers.

PAUL EHRLICH, M.D.

UNIV. OF MICH.

CLINICAL MEDICINE AND SURGERY

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Professor Paul Ehrlich

THERE is little doubt that the outstanding figure in the history of chemotherapy, up to the present time, is the German scientist and investigator, Paul Ehrlich, who was born in the town of Strehlen, province of Silesia, in Prussia, on March 14, 1854, and died, while still practically in the prime of life, in 1915.

Most of Ehrlich's forbears were business men, but those who still believe in the inheritance of mental characteristics like to cite the fact that his paternal grandfather was a deep student of botany and physics and lectured on these subjects, while Karl Wiegert, the pathologist, was his cousin.

To some it may seem strange that, during his school days, in the gymnasium at Breslau, Ehrlich was considered practically a failure as a student. This, however, is not particularly unusual. The same thing was true, for instance, in the case of Charles Darwin.

He refused, however, to give up the pursuit of his scientific studies, particularly those having to do with medicine, and studied, in turn, at Strassburg, Freiburg and the University of Leipzig, where, again, he cut classes and neglected the study of the prescribed textbooks (in order to spend more time in the laboratory, trying to work out his own ideas), to such an extent that the authorities of the university refused to give him his degree at the end of the regular course. He stayed on, in spite of that, and continued his work in the laboratory for another year, at the end of which period his discoveries were found to be so original and important that the degree, Doctor of Medicine, was readily bestowed upon him, in 1878.

After his graduation, Dr. Ehrlich served as assistant in the medical clinics of Von Frerichs and Gerhardt for several years. In 1889 he was made instructor in internal medicine at the University of Berlin. He received the appointment as director of the Royal Institute for Experimental Therapeutics, at Frankfort, in 1896; was made honorary professor at Göttingen, in 1904; and, together with Metchnikoff, received the Nobel Prize in Medicine, in 1908. His published works, which are fairly numerous and of great importance, tell much of the story of his varied scientific career, but not all of it.

All his life Ehrlich was an empiricist and an experimenter, attributing much of his success to his "chemical imagination", although his knowledge of conventional and orthodox chemistry was far from profound. He would conceive what his friends called a wild idea and then, with

absolute concentration upon the work in hand, would labor in his laboratory until he had proved the soundness of his theories.

We are indebted to Ehrlich for a number of the things upon which modern Medicine is based. It was he who, out of his immense knowledge of dyes and their properties, first propounded the theory of the selective affinity of certain tissues for certain dyes, which led to his studies of the staining of cellular material, such as bacteria, in order to facilitate the observation of its characteristics. It was Ehrlich's "triacid stain" which gave us our present detailed knowledge of the cellular elements of the blood.

His interest in the blood led him to consider the subject of immunity from infectious diseases, which he found could be transferred, by means of the blood or secretions, from one individual to another. This discovery led to the production and standardization of diphtheria antitoxin and to the elaboration of the rather complicated "side-chain" theory of immunity which, while still widely accepted, seems to be decidedly less valuable and practical than the much simpler and more readily demonstrable phagocytic theory of Metchnikoff.

Ehrlich's attempts to find a specific for African sleeping sickness drew his attention to the organic compounds of arsenic and when, in 1904, the invention of the dark field illuminator for the microscope permitted a more thorough study of the spirillar organisms of sleeping sickness, relapsing fever, yaws and syphilis, he decided that it should be possible to develop a specific against the last-named universally prevalent disease. His tireless patience and his devotion to his empiric dreams are attested by the fact that he kept on, after 605 attempts in this direction had failed, and on the 606th, in 1910, produced Salvarsan (arsphenamine) which, while not the agent for the *therapia sterilisans magna*, of which he had dreamed, was an enormous advance in the treatment of luetic infection.

Few, if any, men have made so many contributions to the practical side of the basic sciences underlying the practice of medicine as were made by Paul Ehrlich; so much so that it has been said of him: "His uniquely fertile and versatile career of medical research has made him the most original and picturesque investigator of medical science."

The value to posterity of the projection of a given personality is directly proportionate to the amount of cultivation work done on the raw material *by its possessor*.—Dr. George Draper.

Chemotherapy

IN *DEFINING* the word, Chemotherapy, the lexicographers differ. Dorland says that it means the administration of certain chemical substances, usually parenterally, with the idea that they will exert a specific toxic effect upon certain definite microorganisms, without damaging the cells or tissues of the host. Stedman defines the word, more reasonably, as "The treatment of disease by chemical substances or drugs."

Because certain physicians still think of this subject from Dorland's point of view, it seems worth while to consider, briefly, why this position, if it was ever tenable, is so no longer.

Quinine and mercury are generally looked upon as typical examples of specifics, for the treatment of malaria and syphilis, respectively, but a bit of consideration will readily show that neither is free from definite and sometimes toxic effects upon the host; nor, for that matter, is arsphenamine, which has been classed as one of our newer specifics, but which acts upon a number of disease-producing organisms besides those of syphilis and alters body chemistry.

An interesting fact, which has now been shown by a number of workers, is that all of the drugs in this list, including mercurochrome, hexylresorcinol, Metaphen, manganese butyrate and a number of others, when injected intravenously or intramuscularly, cause a more or less marked and prompt increase in the number of leuko-

cytes in the blood. Since Metchnikoff, in his monumental work, "Immunity in Infective Disease" declared and proved, to the satisfaction of most reasoning persons, that the white blood cells are the chief, if not the only, factor in recovery from infections (a position which is being ably defended, from the clinical standpoint, by Ferguson), there seems reason to believe that the favorable results following the administration of the remedies mentioned are not by any means wholly specific, but are consequent upon the leukocytosis which all of them produce.

This may be true, to some extent of the salicylates, the iodides and certain other remedies which are now being administered intravenously to a considerable extent, but even if it is the case, they have other direct and demonstrable effects upon the nervous system or other structures. It may also be true, in considerable degree, of the serums and vaccines, whose action, while it seems to be fairly specific, in certain cases, is by no means always strictly so.

When it comes to the administration of the salts of calcium, iron, and other minerals, which have well recognized tissue-reconstructve properties, and such biologic products as insulin for diabetes and liver extract for hypertension, the part played by the leukocytes is probably minimal, the favorable effects of these remedies seeming to rest upon a chemical, rather than a biologic basis.

In the time of our grandfathers, Chemotherapy, even in its broader sense, was largely empiric. They gave certain drugs for "rheumatism", "inflammation of the bowels", "colic" or "fits", because somebody or other, in experimenting with all the remedies in his saddle-bags, thought he had seen a favorable response from their use in these supposed disease entities, which we now recognize as being merely symptoms of a variety of underlying causes.

We still have to do a certain amount of clinical experimenting, in many cases, but it now has a sound, scientific basis. Practically all new drugs now offered to the profession are carefully worked out upon animals, as to their physical, chemical and physiologic effects before they are put on the market, so that the physician who uses them needs to do no stabbing about in the dark. Many of the old drugs, long used empirically, have now been placed on a scientific basis in the same manner.

A generation ago, the attitude of the socalled leaders of the profession—and, in an exaggerated form, of the eager, "me too" followers—was one of "therapeutic nihilism". Surgery was regarded as the only "scientific" method of treatment.

Modern researches and discoveries, in chemistry, pharmacology, biology and various other sciences, have made r a d i c a l changes in our feeling toward drugs. Today, the man who studies these indispensable weapons in his therapeutic armamentarium can apply them with a precision and certainty unimaginable half a century ago.

The popularizing of the hypodermic syringe as an instrument for drug administration, and the perfecting of a wide range of remedies suitable for subcutaneous, intramuscular and intravenous injection, have eliminated the factors of uncertainty in the individual absorptive powers of the gastrointestinal canal, which are inevitably present when drugs are given by mouth.

We seem to be at the beginning of a new era of accurate and scientific chemotherapy. New and powerful drugs are being given to us almost weekly; our old favorites are being confirmed to us, with the seal of the pharmacologic laboratory upon them; and new and improved methods of administration are at our disposal.

If we would check the inroads of the irregulars, we must keep abreast of this newer knowledge and fit ourselves to be, in truth, Doctors of *Medicine*, for there the healing cults cannot follow us.

No amount of experimentation can ever prove me right. A single experiment may at any time prove me wrong.—Albert Einstein.

The New Dress

THE most delicious meal in the world will not arouse hunger strongly unless it is served in an attractive and appetizing manner.

Even a beautiful woman is more charming if she is appropriately and becomingly dressed.

We believe that we have been giving our readers a sound and sustaining intellectual and professional meal every month, pleasingly served, but we feel that the banquet we are providing deserves an even more dignified and beautiful setting, and this we have striven to give it.

The August number was set, in part, in the new type and with the new headings. In the September issue these were used throughout, and the new cover now appears for the first time. It may be desirable to make some slight alterations later, if, by so doing, we can make our pages more sightly and readable.

If you have been fond of us as we have hitherto appeared, we hope you will admire us even more in the new and modern dress and will find us more attractive and constantly more serviceable to you.

If you have not as yet received us as a regular visitor, we feel that our appearance is now such that you will be proud to have people see us in your office and to introduce us to your most particular and critical friends.

If you can think of ways in which we can make ourselves handsomer or more useful to you, we shall welcome your suggestions.

The person who is satisfied can never perceive truth.—J. Krishnamurti.

The Physician's "Customers"

MOST physicians speak of those who seek their professional services as patients; some call them clients, borrowing the legal phrase; a few of the older men, especially in rural districts, still allude to them as "patrons"—a hold-over from medieval times, when the man of medicine was a hanger-on at the court of some prince or noble, on a parity with the jester and the "clark", and rendering service to the person and family of his "patron".

Of late, sport reporters have adopted the custom of describing those who part with their shekels to purchase the privilege of witnessing pugilistic encounters, as "customers". It sounds peculiar, at first (and doubtless was used for that very reason), and would, perhaps, appear even more unusual if applied to the people who call upon the physician for help; but there would, we believe, be certain points of merit in thinking of the doctor's "customers".

In the first place, if the physician thought of his patients as customers, he would visualize them as persons who came to him to buy something (his expert services) which they considered to be worth money—like shoes or shirts or golf balls or cigars; and, realizing that he had a valuable commodity for sale, he would have no hesitation in discussing its price with his "customers" and arranging for a prompt and business-like payment of the account.

So long as physicians think of their patients as "patrons", they can scarcely help feeling that these people are doing them a favor when they seek professional advice; and to ask them for money seems almost as if the friend who has entertained one overnight should demand payment for board and room in the morning. We will never cease to deserve the reproach of being "poor business men" until we begin to *think* of our patients as customers—whether we *call* them that or not.

But there is an even more important side to this question. The merchant who allows his shelves to become cluttered up with a stock of antiquated goods will soon find that the shadow of a purchaser rarely darkens his doorsill. Most of them realize this and when, through poor judgment in buying, such a condition occurs, they hasten to unload the slow-moving articles, even at a

financial sacrifice, so as to make room for merchandise which will attract customers to their places of business. The annual inventory gives them valuable information along this line.

How many physicians ever stop to take an inventory—not of the drugs, instruments and apparatus in their offices (these are only working tools, not the things they sell to their patients), but of the stock-in-trade of ideas, knowledge, skill, tact, courtesy, sympathy and the like, for which they expect their "customers" to pay them money?

Such an inventory would, we fear, reveal, in some cases, a mass of frowsy, shop-worn, out-of-date items, heavy with the dust of carelessneess and inertia and musty with the mildew of ancient tradition and usage. How can one expect people to pay good prices for things like these? If we are catering to "customers", we must fill our warehouses with strong, substantial, serviceable, valuable goods; not showy, tinselly things which will catch the eye, but such as will give continuing satisfaction, year after year.

The dumping of the old, moth-eaten, unserviceable stuff will entail no financial loss; but the sacrifice of preconceived notions, pernicious habits, cherished superstitions and prejudices and other such will be more painful than the cut prices on any post-inventory sale. Out they must go, however, in order to make room for the new merchandise which will be supplied by diligent study of modern textbooks and sound professional periodicals, and by attendance at postgraduate courses and medical society meetings.

When the new stock is in, the prices must be marked in accordance with the intrinsic worth of the articles, and *these prices must not be cut.* If we feel that someone, who is unable to pay the price and who is outside the reach of the constituted charitable agencies, is in dire need of our services, let us *give* them, but not cut prices. There is, and of course must be, an elasticity in adjusting the fees for major professional labors to the circumstances of the patient, which would be abhorrent to a modern merchant, but the charges for house and office calls and other minor services should have a high degree of stability and regularity.

Every citizen may be entitled to sufficient food to maintain life, clothes to cover his body and shelter from the elements, whether he earns these things or not. At any rate, the charitable organizations and most communities endeavor to furnish them to the destitute. But no one has ever claimed that all men and women have a right to demand automobiles, silk pajamas and artichokes.

Essential medical care is provided to the indigent, in cities by the free clinics, and in rural districts by the county poor commissioners. There is no more reason why they should have a claim upon the most highly skilled and valuable medical services than there is for furnishing them, free, with *crêpe de chine* chemises and strawberry shortcake. A man has to think whether or not he can *afford* a grand piano or a suit of evening clothes. Why should it be unreasonable that he give equal consideration to his financial ability to employ the highest type of medical attendant?

But if our patients are "customers", they are likely to inspect the commodities they are about to purchase, with a painstaking scrutiny heretofore unknown, and buy where they will receive the most real value for their money. So the thing works both ways.

There is really much food for long and penetrating thought in this question of the physician's "customers".

The man who never alters his opinions is like standing water, and breeds reptiles of the mind. —William Blake.

Harvest Time

THIS is the time of year for the good, old-fashioned harvest festivals—the time when the farmers are gathering in the fruits of a year of patient toil and feel, very properly, that they have occasion to rejoice and relax a little.

The planting of the seed was done long ago—the wheat last autumn; the corn, oats, potatoes and other things during the springtime that is past. Without that planting, there would now be no harvest.

After the seed was sown there was a long period of patient waiting. The farmer, no matter how diligent and eager he may be, cannot *grow* the seed. The processes of Nature must do that, in their own good time and way, and they do it quietly, unostentatiously, but *inevitably*. All that the husbandman can do is to see that the seed is good, that the soil is appropriate and properly fertilized, and that, when the tender shoots appear, the crop is regularly and thoroughly *cultivated*, until its maturity.

We may not be planting and cultivating beans and hay and onions, but we are, none the less, growing crops, of a sort, in the fields of our lives, and the laws of Nature apply to them, just as they do to the farmer's crops—and everything else in the universe, for that matter.

First comes the soil; and we haven't much to say about that, for the germ-plasm of our parents and our antenatal conditions provided it, in the first place. We can, none the less, do a good deal to improve conditions, when we have learned what to do and how to do it. We can fertilize the soil with proper exercise, food, rest, recreation and the like, so that what looked in the beginning like a stony and unprofitable field can be made to produce a very satisfactory crop.

Then the seed. A good deal of it, including some of the most important varieties, was sown by others (our parents, teachers and associates, in our early years); and sometimes what they sowed proves to be Canada thistles and dodder, when it comes up. But even a weedy field can be reclaimed by tireless and intelligent effort, and when we get those earlier crops (wild oats, perhaps) out of the way we can plow the field deep, so as to turn under all the old stalks, and plant it again with seed of our own choosing.

The waiting time is the hardest time of all, for most of us, for we are an impatient crew and are tempted to dig down and see whether the seed is sprouting. It is of no use. Nature works slowly and imperturbably, but always accurately. If the soil and the seed were right, the crop will be in exact proportion to their rightness.

When the seeds begin to sprout, the cultivation must begin at once and it must continue, regularly and systematically, throughout the growing season. If it is started late, the results will never be so good, but the case is not hopeless. It is far better to begin late than not at all.

For us this means the daily practice, not only of those thoughts and acts which have to do with our particular line of work, but also all manner of kindly, helpful and courteous things — thoughts and deeds which will make the world a pleasanter place for all the people with whom we come into contact. Such activities will crowd out and kill the weeds of selfishness, jealousy and false pride.

If we carry out this program *now, today*, we need do no worrying. The past—our past—which *we* have made, is beyond our reach. The future is nothing, as yet. When it arrives, in small, daily installments of 24 hours each, we call it today—*the only day we have to live*. All we have to do is to sow the seed—just the kind of seed we choose — and cultivate it assiduously.. Nature will do the growing, according to her wise and unvarying laws, and the harvest is *sure* — the reaping of exactly what we have sown.

LEADING ARTICLES

The Present Status of Chemotherapeutic Research in Syphilis*

By George W. Raiziss, Ph.D., *Philadelphia, Pa.*
Professor of Chemotherapy, Graduate School of Medicine, University of Pennsylvania

DUE to its important accomplishments in the therapy of various infectious diseases, particularly syphilis, chemotherapy has, in the last quarter of a century, attracted the world-wide attention of scientists. This science is rightfully considered most likely to afford more hopes for progress in the cure of infectious diseases than any other branch of medicine. Its only rival is serum therapy, which, however, has its natural limitations. Chemotherapy possesses practically unlimited possibilities, due to the fact that its main function is to create and test new chemical compounds. It is fundamentally interwoven with synthetic chemistry, and the domain of the latter is practically boundless, because chemical elements can be almost indefinitely combined with each other, forming new molecules possessing new physical, chemical and therapeutic properties. The element carbon is endowed with the ability to combine probably to a greater extent than any other element. Chemical compounds containing carbon constitute the field of organic chemistry. Arsenic can be readily combined with carbon, and hundreds of compounds containing the two elements are already known. Many of the latter derivatives have valuable therapeutic properties. Hundreds of additional arsenical compounds can and will be prepared and, no doubt, among them will be found many of therapeutic value.

Since chemotherapy offers great hopes for the treatment and eradication of infectious diseases (general septicemia, pneumonia, tuberculosis, etc). which, at present, cannot be combated by known remedies, it has therefore become popular and is attracting the attention of physicians, scientists in general and even the laity. Considerable confusion arises from the inclusion of many problems of research under the head of chemotherapy. Often subjects of investigation and data obtained in research are classified as chemotherapeutic researches, but actually they do not belong to this field. Therefore, it is important to attempt to define what is actually chemotherapy.

No doubt Ehrlich and his collaborators contributed more to chemotherapy than any other group of scientists. Indeed, it was Ehrlich who coined the word "chemotherapy" and made an attempt to suggest a definition of this science. On the basis of the theoretical considerations and experiments performed by Ehrlich, and also on the basis of the work carried out by most of the men engaged in chemotherapeutic research, I believe that the following requirements must be embodied in the definition of chemotherapy.

What Chemotherapy Is

First: The specific field of this science—the field in which it operates and should operate—is the large group of diseases caused by pathogenic microorganisms. Diseases, the foundation of which is not an infection, should not be included in chemotherapeutic research.

*Contribution form the Dermatological Research Laboratories, Philadelphia, Pennsylvania.

Second: The essential factor of this type of research is the elaboration of new chemical compounds involving synthetic chemistry.

Third: Chemotherapeutic research should be based on rational lines. The chemical compounds to be investigated should not be selected empirically, but on the basis of scientific theories and, particularly, according to rules representing a relationship between chemical constitution and toxicologic and therapeutic effects.

Fourth: The toxicologic and therapeutic values of the new compounds should be determined by extensive experiments upon lower animals, which include both normal animals and those infected with pathogenic microorganisms.

Fifth: The clinical trial of new chemotherapeutic agents should be carried out in institutions equipped with the facilities and the organization necessary for the performance of strictly scientific clinical experimentation. Here the basic requirement is to refrain from undertaking the clinical investigation of any product which in the laboratory has not been first found to be a comparatively non-toxic and definitely therapeutic agent. Chemical compounds for the treatment of a certain infectious disease should not be considered worth while unless they show definite curative effects in the infectious disease created experimentally in animals.

Progress In the Laboratory Methods Employed for the Evaluation of Chemotherapeutic Remedies

Ehrlich and his coworkers created the basis for the experimental evaluation of chemotherapeutic agents. They worked with various types of trypanosomes inoculated into mice; e.g., the spirochete of relapsing fever in mice and rats, chicken spirillosis and the spirochete of syphilis in rabbits[1]. Since then, in testing new chemical compounds, much progress has been made in the selection of other pathogenic microorganisms for the inoculation of lower animals. The laboratory methods for the transmission of infectious diseases into animals were also further investigated and standardized to a greater extent.

There are found in the scientific literature many discrepancies, rendering the results of different investigators incomparable. For instance, the minimum therapeutic dose of a certain drug in trypanosomiasis of white rats may be found by one investigator to be 50 milligrams per kilo of body weight; another may find that the same compound has no trypanocidal efficiency at all, or that a dose 3 or 4 times larger is required to produce a curative effect. This discrepancy may be due to the fact that the second investigator inoculated the animal with a greater number of trypanosomes, producing a heavy infection, while the first investigator induced the same disease by employing a small number of trypanosomes, thus causing a mild infection in the animal. Indeed, there is still much work to be done to prevent disagreement in the results and eliminate errors in the conclusions derived from experimental work. The biologic methods for the evaluation of chemotherapeutic remedies are so complicated and uncertain as to make such standardization very difficult.

An unfavorable feature of many tests for the therapeutic activity of drugs is that infected animals may recover spontaneously. On this account, the curative effect cannot be attributed solely to the drug.

Animal Experiments

Mice or rats infected with trypanosomes can be used to great advantage in chemotherapy. Since 1915, Schamberg, Kolmer and Raiziss have been developing methods for the inoculation of white rats with the *Trypanosoma equiperdum* (the parasite of dourine). Kolmer[2] suggested a method for determining the exact strength of the inoculation and also of the infection. He suggested standardizing the infection induced in the rat by diluting the total volume of blood taken for the injection so that it will contain a definite number of organisms. By this method it was expected that the animal to be infected will develop a definite standardized infection.

In 1917, Kolmer, Schamberg and Raiziss[3] inoculated rats with known numbers of *Trypanosoma equiperdum* by this same method and studied the effects produced by the various doses of arsphenamine. In 1922, Voegtlin and Miller[4] suggested a new principle, by which rats were not only inoculated with a definite number of trypanosomes, but, prior to the injection of the drug to be tested, the number of the trypanosomes in the peripheral blood was verified. If the number of trypanosomes is less than 100,000, treatment is delayed until later in the day or even for 24 hours, when the required stage of infection is

attained. The above two authors suggested other modifications which appear to be valuable.

To secure even greater accuracy—since the resistance of the trypanosomes may fluctuate—at the International Conference on Biological Standardization, held under the auspices of the League of Nations, at Geneva, in 1926[5], it was decided to make the trypanocidal test a comparative one. For each test, two groups of animals should be infected with the same inoculum; one group should then be treated with the drug under consideration, the other with a standard product and the results of the two compared. The tested drug should exhibit a therapeutic efficiency at least as great as the standard.

Raiziss and Severac introduced a modification to the method recommended by Voegtlin and Miller. In our opinion, it increased the exactness of the test. Thus, in addition to reading the results twenty-four, forty-eight and seventy-two hours after injection of the drug, as suggested in the original procedure, we examined the blood of the animals daily for twenty-one days. We were prompted to this course by the observations of Schamberg, Kolmer and Raiziss[6] and others that the disappearance of trypanosomes from the circulation in the first few days does not prove actual sterilization of the animals, as the organisms may subsequently be found again in the blood.

From the results of our 100 tests, carried out according to the standard method, we believe that arsphenamine of definite therapeutic quality should sterilize rats infected with *Trypanosoma equiperdum* in a dose of 0.006 to 0.008 Gm. per kilogram, by the intravenous route.

Much fruitful work was performed and considerable progress attained in the very important method of inoculating rabbits with the organism causing human syphilis. Experimental rabbit syphilis became invaluable in the study of new chemotherapeutic agents for the treatment of syphilis. In this country the Nichols strain is used extensively.

Experimental Syphilis in Rabbits

In conducting this test, a rabbit is inoculated intrascrotally or intratesticularly with an emulsion of *Treponema pallidum*, and in the course of 4 to 6 weeks a primary lesion is observed on the genitalia. At this stage the animal receives, intravenously or intramuscularly, a definite amount of the chemotherapeutic agent to be tested. Material removed from the lesion is examined every day for the presence of spirochetes. The complete disappearance of spirochetes from the lesion and later a complete cicatrization of the lesion and, finally, the return of the tissues to a condition of normality, were considered, by earlier investigators, as definite evidence of curative effect. Today, such a result is no longer decisive in the determination of the minimum therapeutic dose. Raiziss and Severac found that many comparatively inactive chemical compounds were able to produce in animals therapeutic results similar to those described above; that is, the disappearance of spirochetes from the lesions and the apparent cure of the animal.

There is no doubt that few chemical compounds can cause the spirochetes to disappear within 24 to 48 hours or effect complete disappearance of large syphilomas of the testicles in the course of a week or two—indeed, this rapid curative effect is characteristic largely of arsphenamine and its derivatives—but a considerable number of chemical compounds inferior to these remedies, used in the treatment of syphilis, will also produce a fairly rapid disappearance of spirochetes and cause the testicular tissue to assume a normal appearance. In a recent investigation Raiziss and Severac[7] found that even such weak antisyphilitic remedies as iodine compounds exert a definitely favorable influence on experimental syphilis and afford asymptomatic effects in spirochetal infections. Accordingly, iodine compounds, from the experimental standpoint, should be pronounced valuable antisyphilitic agents. In reality they are not so curative as they appear at first glance.

In the past, errors were frequently made by investigators in pronouncing certain chemical compounds curative for experimental rabbit syphilis, basing their observations on the disappearance of spirochetes and the involution of lesions. Very decisive progress was made in this field of research when Pearce and Brown[8] showed that, although spirochetes may disappear from lesions under the influence of curative chemical compounds, they continue to lodge in the animal body. These investigators suggested a confirmatory test consisting of the inoculation of control animals with lymph node emulsions derived from the apparently cured animals. While this test, if properly carried out, necessi-

tates the observation of the animal for a period of about 8 months, it is a more rigid method than that employed by the early workers in this field—indeed, it is the only reliable procedure for the determination of the actual value of an antisyphilitic remedy..

For this purpose the animal under investigation is either killed or etherized; an incision is made slightly below the knee joint and the popliteal nodes removed from the lump of fat in which they are imbedded. They are then ground very fine and the emulsion injected into the testes of two normal rabbits If, after 4 to 6 months of observation, the two control animals do not develop lesions in which spirochetes are found, the first animal can be considered fairly definitely cured of the syphilitic infection. Only those chemical compounds which can produce such therapeutic effect, under laboratory conditions, can be rightfully considered eligible for use as antisyphilitic remedies in the treatment of patients.

Rabbit Syphilis in Diagnosis

Today, experimental rabbit syphilis is not only of great importance in the evaluation of chemotherapeutic agents, but lately it has also found application in the diagnosis of syphilis in patients. While the Wassermann test, after having undergone refinement and standardization in the hands of numerous investigators, particularly, Noguchi, Bordet, Kolmer and others, is now indispensable in the diagnosis of human syphilis, permitting an accurate recognition of both early and latent stages of the disease, it requires, in some obscure cases, the support of another test.

Chesney and Kemp[9] suggested the application of experimental rabbit syphilis in the diagnosis of human syphilis. They made use of the observation that syphilis may be transmitted from infected human beings to rabbits by intratesticular inoculation of the latter with emulsions of the lymph nodes of the former. Observations were made with 3 patients. In case one, the lymph node excised before treatment gave rise to syphilitic orchitis in both inoculated animals. After treatment for a full year, all clinical manifestations of syphilis disappeared and the Wassermann reaction became negative. At this time a second node, after excision and inoculation failed to produce an infection in a normal rabbit. With two other patients negative results were obtained by a similar technic.

Further work in this direction is very desirable, since it will help in the accumulation of data as to the possibility of the cure of syphilis. Syphilologists have much faith in the Wassermann test, which for many years proved to be a reliable guide in the diagnosis and treatment of the disease, but there are cases where it is very desirable to have a check on this test. The procedure adopted by Chesney and Kemp is of great importance as a further control on either positive or negative Wassermann tests.

In the course of experimental work on animals, chemotherapeutists frequently extend their researches into other related fields. Studies of rabbit syphilis have yielded a wealth of information concerning the mechanism and rapidity of infection and the course and character of the disease. Since the causative organism, *Treponema pallidum*, was obtained from human syphilis, results observed in the rabbit may be rightfully utilized for the explanation of phenomena seen in syphilitic patients. In this way much light was thrown on such problems as the rapidity with which syphilis spreads in the human body, the penetration of the spirochetes into the central nervous system, the asymptomatic course of the disease and the possibility of reinfection.

Rapidity of General Infection

Of particular importance are recent findings indicating the great rapidity with which spirochetes travel in the animal body. Brown, Pearce and Witherbee[10] found that, when rabbits are inoculated with spirochetes intrascrotally, the organisms can be recovered from the inguinal lymph nodes within the next 48 hours; and from the blood stream within one week, when inoculated intratesticularly. It is significant, then, that spirochetes invade the animal body "at a period well in advance of the appearance of the primary lesion"[11].

The observations of Brown and his coworkers were confirmed in a still more striking manner by Kolle and his collaborators, who demonstrated that the spirochete of syphilis travels with great rapidity in the animal body. Kolle and Evers[12] disclosed that as early as 30 minutes after scrotal infection, the inguinal lymph nodes of rabbits contain spirochetes. Even more

striking were the data obtained by experiments on guinea pigs, in which spirochetes were found in the lymph nodes as early as 5 minutes after inoculation.

The question of the penetration of spirochetes from the genital lesions into the deeper structures of the body and, particularly, into the central nervous system. which is of importance for the comprehension of neurosyphilis in patients, was approached experimentally by Brown and Pearce[13] who inoculated rabbits with spirochetes through the testicles and were subsequently able to demonstrate the penetration of the organisms into the spinal canal by injecting some of the latter into the testicles of healthy animals and producing typical syphilitic lesions. Raiziss and Severac[14], on the other hand, were able to secure definite evidence of general syphilitic infection after the introduction of spirochetes into the fourth cerebral ventricle of rabbits. It was found that such an infection is produced in the majority of cases. Of particular importance is our observation that, in the greater number of animals, the lesions appear in the testicles. Thus, while Brown and Pearce found that in rabbits the spirochetes migrate from the site of the testicular inoculation into the intraspinal canal and generally into the cerebrospinal system, our experiments definitely proved that they travel from the cerebrospinal system to the superficial tissues, particularly the testicles.

Other Animals Susceptible to Syphilis

Animal experimentation also disclosed numerous facts relating to the problems of asymptomatic syphilis, a condition so frequently encountered in patients who have practically no symptoms of the disease and still harbor spirochetes, as shown by a positive Wassermann test or, later on, by actual manifestations of the infection.

Kolle and Schlossberger[15] found that mice and rats can be inoculated intrascrotally with syphilis in an asymptomatic form. Previously, it was generally accepted that the rabbit was the only lower animal susceptible to syphilitic infection. Now it is recognized that mice, rats and guinea pigs can acquire syphilis. For six or eight weeks after the inoculation with spirochetes, mice seemingly remain free of infection; at least it is so weak, that the presence of spirochetes cannot be proved. After two months, however, the lymph nodes of these animals, as well as the brain, spleen and other organs, harbor spirochetes. Emulsions of these organs inoculated into rabbits produce syphilitic lesions. Thus, in inoculated mice, the spirochetes not only remain alive in all cases, but in time multiply as well, without, however, producing outward manifestations of syphilis.

Reinfections

Considerable attention was directed by syphilologists upon the problem of reinfection. For many years the general contention was that a patient once syphilitic will remain so forever, and, furthermore, that while harboring spirochetes in the body, the syphilitic could not be reinfected. The above observations were made by clinical methods and were adopted as a foundation for experimental work. Animals were considered as harboring spirochetes if they could not be reinfected; if reinfection could be produced, then they were considered originally free of spirochetes; i.e., they either had not acquired the infection or had been subsequently cured.

Kolle and Schlossberger[16] and Kolle and Evers[17], Chesney, Halley and Kemp[18] and other workers, in a series of ingenious experiments, proved that reinfection, or better, superinfection, is actually possible in infected animals. It is true that the animals do not develop a new testicular lesion while they still harbor spirochetes of the first infection. They seem to possess an immunity, but this is only a chancre immunity which does not prevent the parasites from penetrating the body. Such immunity is only an asymptomatic infection. In other words, *animals can be infected a second time while carrying the original infection.*

This interesting finding may be of considerable value in the interpretation of the course of the disease in human beings. A patient with a quiescent form of syphilis, due either to the antisyphilitic treatment which arrested the infection or to the asymptomatic character of the disease, and harboring spirochetes in the deeper structures of the body, may be reinfected, the second infection again assuming an asymptomatic course.

Further progress in these interesting studies, which are so closely related to chemotherapy, will no doubt enable us to understand syphilis much better, clinically. Furthermore, the study of other infectious diseases may be benefited by acquiring new methods of research as well as new facts concerning the general mechanism of infection.

The View Point of Clinicians Regarding the Value of Arsphenamine and Its Derivatives in Syphilis

A little less than ten years of the arsenical era were devoted to the trial of arsphenamine in the therapy of syphilis and another decade has elapsed since neoarsphenamine was introduced. The former is used today by a comparatively small group of syphilologists, who consider it more curative and expect a more lasting therapeutic effect from it. The majority of those treating syphilis, however, are greatly in favor of neoarsphenamine, due to the simplicity of administration and particularly to the greater safety for the patient. Arsphenamine causes more nausea and vomiting, with greater incidence of nitritoid crises, jaundice and other major complications accompanying arsenical therapy. No doubt neoarsphenamine is considerably less toxic than arsphenamine, as evidenced by animal experimentation. Considering the large number of intravenous injections of the arsenicals which modern syphilotherapy requires for individual patients, and also in view of the undermined physical condition of patients suffering from latent syphilis, the greater safety of neoarsphenamine is an important consideration.

While arsphenamine is more uniform in chemical composition, and its therapeutic effect, as shown experimentally on animals, is higher, it should not be overlooked that neoarsphenamine is chemically and biologically closely related to it. Neoarsphenamine represents merely the addition of sodium formaldehyde sulfoxylate to the arsphenamine molecule. Therefore, the therapeutic efficiency of neoarsphenamine is essentially that of its parent compound, the difference being only a quantitative one; i.e., more of the former is required to obtain maximum therapeutic results. Clinical observations indicate that results obtained by intensive neoarsphenamine treatment are, on the whole, the same as those secured by the employment of arsphenamine.

In the past six or seven years, a new derivative of arsphenamine, similar to neoarsphenamine, named **sulpharsphenamine,** has been used in the treatment of syphilis. Chemically the difference between the two derivatives is that sulpharsphenamine is formed by the introduction of the methylene sulphonic acid group into the amino radical of arsphenamine, while neoarsphenamine is the results of the introduction of the methylene sulfinic acid group into the same radical.

While the toxicity of sulpharsphenamine, as seen in animals, is about the same as that of neoarsphenamine, its trypanocidal efficiency is lower than that of either arsphenamine or neoarsphenamine. This has been demonstrated by series of experiments performed by Raiziss, Severac and Moetsch[9], on animals infected with *Trypanosoma equiperdum*. The clinical results obtained with sulpharsphenamine were very satisfactory, particularly from the curative standpoint. The new drug, however, gave rise to a greater number of reactions than either of the above mentioned arsenical compounds. The incidence of exfoliative dermatitis was found to be considerably greater; besides, cases of purpura hemorrhagica were reported following intravenous and intramuscular administration of sulpharsphenamine. Occasionally, both reactions were of such severity as to preclude the extensive use of this drug in the therapy of syphilis.

Value of Arsphenamine

In the last few years there have appeared in the literature a number of statements representing a severe criticism of arsphenamine and its derivatives. No doubt the time is ripe for a critical attitude towards the employment of this group of arsenical compounds in the treatment of syphilis. Almost 20 years have elapsed since their introduction into therapy and there is no doubt that they do not represent the final phase of research in chemotherapy. Therapeutically more powerful remedies and also safer preparations should be sought. There is still a great deal to be accomplished in this field, but a survey of the drugs available at present for the treatment of syphilis points strongly to the fact that the arsphenamines are now the best remedies for the treatment of this disease. A valuable summary of the views on this situation can be obtained from the declaration made and signed by 100 German syphilologists, which was published in the *Dermatologische Wochenschrift*, Mar. 3, 1928, and subsequent numbers. Among others, statements made in this declaration were as follows:

"Statistics do not support the contention of some authors that there is an increase in the incidence of general paralysis in the civilized countries, due to arsphenamine therapy. The assertion that insufficient arsphenamine medication is particularly instrumental in the develop-

ment of late neurosyphilis is also baseless. If this were true, an increase in the number of cases of paralysis and tabes would be noticeable by this time because, in the early period of arsphenamine therapy, treatment was rather insufficient, as we now know.

"Neurorecidives, which can be explained by the use of too little arsphenamine, are far less frequent now than formerly.

"That intensive arsphenamine therapy (particularly in combination with bismuth or mercury) yields splendid results in primary syphilis is almost universally acknowledged. Such treatment, when employed for a sufficient length of time, also yields very satisfactory and lasting results in secondary syphilis, including the condition of the cerebrospinal fluid. After prolonged observaton for a number of years, many of these cases may be safely regarded as totally cured."

Bismarsen

In the last five or six years various compounds of bismuth, which was first introduced by Sazerac and Levaditi, have been successfully used in the treatment of syphilis. In addition, certain metallo-organic compounds, such as silver and gold arsphenamines, were elaborated and found valuable, both experimentally and clinically. Raiziss[20] and his coworkers have discovered a new derivative of arsphenamine which is a metallo-organic compound containing both arsenic and bismuth. Bismuth arsphenamine sulphonate—for brevity's sake called Bismarsen—is the sodium salt of a bismuth derivative of arsphenamine methylene sulphonic acid, and corresponds to the empiric formula, $C_{21}H_{21}O_{12}As_2Na_3S_3N_3Bi_2$. This new drug should be administered to patients only *intramuscularly*. By this route, white rats tolerate Bismarsen in doses higher than 400 milligrams per kilogram of body weight.

The drug has been tested experimentally in rabbit syphilis and the results obtained were very satisfactory. Small doses, injected intramuscularly into rabbits with large syphilomas, effected the rapid disappearance of the *Treponema pallidum* from the lesions and complete involution of scrotal and testicular lesions within a short time. A few milligrams of the drug per kilogram of body weight, administered intramuscularly to syphilitc rabbits, caused, in some cases, a complete disappearance of spirochetes within 48 hours after the first injection. No reappearance of the lesions was observed. The method of Brown and Pearce, consisting of the lymph node transfer, further indicated that Bismarsen treatment is capable of completely sterilizing animals. Indeed, the author was greatly impressed with the decisive curative effect which can be obtained by the use of Bismarsen in syphilitic rabbits.

With this preliminary chemotherapeutic data, the drug was used in the syphilis clinic of the Hospital of the University of Pennsylvania for 21 months, during which period more than 4,000 injections were given to 204 patients.

Stokes and Chambers[21] made an extensive study of this new preparation, administering it to patients in 0.2 gram doses, intramuscularly. The drug is dissolved in 1 cc. of sterile distilled water, forming a yellow-brown solution, to which is added 2 minims of a 2 percent solution of Butyn, as a local anesthetic. When a careful epifascial method of injection is used; e.g., the method described by Stokes[20], Bismarsen is tolerated by patients, with slight, temporary, local pain.

It was found by Stokes and Chambers, and also by others, that the drug has a low toxicity, from the clinical standpoint. In 4,200 injections, 3 nitritoid crises were observed, which were controlled by the use of epinephrin and atropine. In the same number of injections no exfoliative dermatitis occurred. It is interesting to know that patients who exhibit cutaneous reactions following arsphenamine or neoarsphenamine can occasionally tolerate bismuth arsphenamine sulphonate without reaction. In general, Stokes and Chambers think that the drug may be considered as causing little cutaneous irritation—much less than sulpharsphenamine. They also found that it has marked tonic properties; patients, as a rule, feel better and increase in weight after Bismarsen therapy.

A most interesting factor concerning the antisyphilitic therapy based on the use of Bismarsen, is its favorable influence on serologic reactions. Those who have employed the drug extensively are very much impressed with its decisive influence on the blood Wassermann test and the spinal fluid. In this connection a quotation from the paper published by Stokes and Chambers is illuminating:

"The expectancy for an effective combined arsphenamine (not neoarsphenamine) and mercurial therapy, as indicated by our experience, is approximately the securing of a negative blood Wassermann reaction by the eighth week (from the eighth to the eleventh arsphenamine injection), so that the new drug, bringing about a negative reaction in from fourteen to sixteen injections, unaided, lags only slightly behind the most vigorous present-day methods.

"It is a striking fact, in contrast with reports of as high as 23 percent resistant cases in the literature, that, with three laboratories controlling the serologic results, not one of the 42 patients with early syphilis thus far treated has proved Wassermann-fast. Not a single patient has given a positive Wassermann reaction at the end of his first course of twenty injections, though three have had subsequent relapses . . . .

"In 28 patients thus far examined, at periods ranging from two to four months, after treatment with the new drug was begun, not one has shown an abnormal spinal fluid. One patient showed a 'reversed Kolmer' (--44), which was not supported by the other three tests and was probably a laboratory error. This is truly a remarkable record, if sustained."

Private communications received by the writer of this paper indicate that Bismarsen appears to have a definite place in the therapy of tabes dorsalis and that its effects are favorable in neurosyphilis. Further studies, both from the experimental and clinical sides, have been completed and the results are being prepared for early publication.

New Pentavalent Compounds of Arsenic Employed in the Therapy of Syphilis

The early workers in chemotherapy, under the leadership of Ehrlich, were greatly impressed with the therapeutic efficiency of the arsphenamine group; that is, the trivalent compounds of arsenic. The pentavalent arsenicals are, indeed, much inferior in their therapeutic effect upon trypanosomes and spirochetes and it was rational for Ehrlich and others to concentrate their attention on the trivalent series, while the pentavalent compounds were neglected. In addition, it was observed that practically all pentavalent arsenicals showed a destructive effect upon the optic nerve. Cases of optic atrophy and actual blindness were observed following the intravenous injection of atoxyl, which is, chemically, the sodium salt of paraaminophenylarsonic acid, and of arsacetin, which is the acetyl derivative of the above compound.

It is unfortunate that it became necessary to abandon the pentavalent arsenicals, due to a lower therapeutic effect and the danger of optic atrophy. The chemical properties of the pentavalent arsenicals permit the preparation of many more derivatives than do the trivalent compounds. The former are much more stable and allow the chemist to modify their chemical constitution more extensively than is possible in the latter series.

For a time it appeared that investigation of the trivalent arsenicals had been exhausted and that no further headway could be made. Therefore, in recent years, chemotherapeutists revived interest in the pentavalent organic arsenic compounds. In consequence of numerous attempts to find superior remedies for the treatment of African sleeping sickness and syphilis, several new products became the subject of laboratory and clinical investigation.

As a result of our own work and that of others, it was noted that the toxicity, as well as the curative power, of organic compounds of arsenic depend considerably upon whether or not the amino groups are free or substituted. By substitution in the amino group of paraaminophenylarsonic acid, new remedies such as tryparsamide and amino-arsono-ethanol were prepared. Chemically, tryparsamide is the sodium salt of N-phenylglycineamide-4-arsonic acid. It was synthesized in 1915 by Jacobs and Heidelberger[23]. The biologic properties of the drug were described by Brown and Pearce[24].

Tryparsamide

The trypanocidal as well as the spirocheticidal power of tryparsamide is low and, therefore, this drug was not considered valuable in early trypanosomiasis or early syphilis. However, due to the work of Lorenz, Loevenhart, Blackwenn and Hodges[25], the drug is recognized as being effective in neurosyphilis, particularly in general paralysis. The above authors reported that the clinical and serologic improvement in early and violent cases of paresis is very marked. Some patients fully recovered their normal mentality when treated with intravenous injections of large doses of tryparsamide (from 3 to 5 grams per dose).

A serious drawback to tryparsamide therapy in neurosyphilis is the production of injury to the optic nerve. According to some reports, more or less marked disturbance in vision takes place in almost 7 percent of cases. The clinical investigation of tryparsamide has now become very extensive, and while opinions differ, as yet, regarding the degree of efficacy of tryparsamide treatment, the observers agree that this drug constitutes a definite progress in the treatment of paretics.

In this connection it is interesting to review the statements made recently by Lorenz[26]. The types of cases treated in-

cluded general paralysis, taboparalysis, asymptomatic paralysis, meningovascular syphilis and, to a less extent, tabes. The results are permanent for at least 5 or 6 years. Reliable information as to the present condition of 317 patients was obtained. Of a total of 152 individuals who had been considered recovered, 4 have since died and 14 have returned to state hospitals, so that 134 or 87 percent have continued without relapse for 5 or 6 years. Lorenz believes that tryparsamide and mercury offer a convenient and remarkably effective treatment.

That general paralysis, particularly in the early stage, is favorably influenced by tryparsamide, follows also from the reports from the Mayo Clinic by Stokes and Wilhelm[27] and by O'Leary and Becker[28]. Of 50 cases reported by the latter, the cerebrospinal fluid became totally negative in 10 and showed improvement in 16, while the blood Wassermann became negative in 8. The results in tabes dorsalis were rather discouraging. O'Leary and Becker are of the opinion that, in order to obtain serologic improvement with tryparsamide, prolonged treatment is necessary. This is in accord with the view of Solomon and Viets[29] who state: "In the majority of cases of parenchymatous neurosyphilis, fifty or more injections have been required to produce serologic improvement."

Author's Own Researches on Pentavalent Arsenicals

The chemical constitution of an important pentavalent arsenical is β-(p-arsono phenyl)-amino-ethanol, which for the sake of brevity, is called **arsono-ethanol.** The drug was synthesized by Rodewald and Adams[30]. Closely allied to it is another valuable drug, chemically β-(3-amino-p-arsono phenyl)-amino-ethanol, called **amino-arsono-ethanol,** and synthesized by Adams and Volwiler. Raiziss and Gavron[31], by substitution of two amino groups in hydroxyphenylarsonic acid, prepared 3, 5-diamino-4-hydroxyphenylarsonic acid, to which the name **arsonodiacetyl** was given.

The three new pentavalent organic compounds of arsenic—arsono-ethanol, amino-arsono-ethanol and arsonodiacetyl—have been studied by Raiziss, Severac and Moetsch[32], with regard to toxicity and therapeutic efficiency in trypanosomiasis of rats and in experimental rabbit syphilis. Two of these compounds are considerably less toxic than arsanilic acid, when given intravenously to rats or rabbits, and may be considered additions to the list of compounds superior to arsanilic acid. Insofar as toxicity is concerned, they are about equal to tryparsamide. The trypanocidal effects of these two products are considerably less than that of arsphenamine or arsanilic acid; they are practically equal to that of tryparsamide.

Despite its therapeutic ineffectiveness in experimental rabbit syphilis, tryparsamide is, nevertheless, claimed to exert a favorable effect upon paresis. It seems as if we have no experimental means of determining the therapeutic efficiency of antisyphilitic agents in paresis. The new compounds also failed to show any notable efficiency in experimental rabbit syphilis, yet they, too, may have a favorable influence upon paresis. At any rate, their low toxicity warrants a clinical trial.

Further substitution in the amino groups resulted in the elaboration of Stovarsol **(acetarsone),** which is 3-acetylamino-4-hydroxyphenyl-arsonic acid, prepared and investigated by Fourneau, Levaditi and others[33]. The most interesting observation in connection with stovarsol is its use as a *prophylactic* in syphilis. Some authors claim that they were able to prevent syphilitic infection by the oral administration to patients of one gram of this drug on three successive days (Levaditi[34], Oppenheim[35], Poole[36]). There are some syphilologists who generally advocate Stovarsol for the internal treatment of spirochetal infections. Favorable results with the same compound were also reported in the treatment of amebic dysentery, malaria, and other diseases caused by protozoa.

Conclusion

The impetus which the discovery of arsphenamine gave to chemotherapy resulted in a truly remarkable development of this science. While 25 years ago practically the only remedy available for the treatment of syphilis was mercury, today the armamentarium of the syphilologist includes the three specifics of the trivalent series of arsenicals; namely, arsphenamine, neoarsphenamine and sulpharsphenamine.

To this group of highly potent antisyphilitic remedies was recently added Bismarsen, a derivative of arsphenamine containing bismuth in metallo-organic combination.

Another group of organic arsenic compounds, representing the pentavalent series, has aided materially in the treatment of special forms of syphilis, such as late

neurosyphilis. Of special importance is the drug, tryparsamide. Stovarsol (acetarsone) revived the hope for the preventive treatment of the disease.

Chemotherapeutic methods of research stimulated another brilliant discovery, that of bismuth. Today various bismuth compounds are of invaluable service to the physician. This remedy is comparatively safe and permits of the treatment of the patients for longer periods of time, intensifying and insuring the results obtained by the use of the organic arsenicals.

With the addition of the old remedy, mercury, and other metals, such as silver and gold, the physician today has much greater hopes for the cure of syphilis, and the future is promising for the eradication of this disease which has been a menace to society for centuries.

The methods of research employed in chemotherapy are built on the broad basis of experimental sciences which assure further progress. Chemotherapy hopes for the conquest of infectious diseases in general. Consistent efforts are being made by many scientists today to introduce methods employed in the chemotherapy of syphilis into the study of numerous compounds intended for the treatment of various types of septicemia, pneumonia, tuberculosis and other devastating diseases, for which at present there are no efficient remedies available.

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The MENTAL faculties of man cannot handle the present immense mass of knowledge. We must use the intuition, which is awakened by an appeal to the highest and purest emotions—the serene emotions, such as are aroused by hearing fine music or viewing a glorious sunset.

This is the new technic of education. We must teach creation through art.—C. *Jinarajadasa.*

The Technic of Syphilis Therapy

By Loyd Thompson, M.D., F.A.C.P., *Hot Springs National Park, Ark.*

WHILE the treatment of syphilis is not entirely confined to chemotherapy, inasmuch as hygiene, balneotherapy and diet play an important rôle, the administration of drugs by injection, particularly specifics, in one form or another of the metals, mercury, arsenic and bismuth, constitutes by far the greatest part of the modern therapy of this disease. It is, therefore, with the technic of the injection of the above mentioned specifics that the present paper deals.

Mercury

The use of mercury in the treatment of syphilis dates back at least to a time prior to Fracastoro, for in his immortal poem, "*Syphilus sive Morbus Gallicus*", published in 1530, he writes, "As a fact, the action of mercury on the scourge is marvelous." Buret states that the Chinese, as far back as 2637 B.C., prescribed mercury frictions in the treatment of syphilis.

However, it was probably Hebra, as late as 1861, who first employed mercury by injection, although it was not until after the appearance of Lewin's work, in 1869, that the hypodermic treatment of syphilis became at all popular. Since that time this method of medication has been used extensively, and many different preparations of mercury have been employed. At first the injections were all given subcutaneously, and frightful abscesses sometimes followed; but, according to Lambkin, Balzar, in 1888, pointed out the advantages of deep intramuscular injections, and since that time this method has grown until today it is practiced almost to the exclusion of the subcutaneous route.

The preparations of mercury used for intramuscular injections in the treatment of syphilis may be divided into the soluble and the insoluble preparations. Of the former the *bichloride*, the *benzoate*, and the *succinimide* are most frequently employed; while of the latter the *salicylate* is the one which is the most popular.

The bichloride of mercury may be used either simply as an aqueous solution with a little sodium chloride added, or in an oily base. The latter, which is put up in convenient collapsible capsules by one of our leading manufacturers of pharmaceuticals, is very satisfactory. The dosage is from 0.0162 to 0.0324 Gm. (¼ to ½ grain).

The benzoate of mercury, prepared according to the following formula, has given excellent results in my hands:

Hydrarg. benzoat.	2.0
Sodii chlorid	2.5
Novocaine (procaine)	0.5
Aqua destilat.	100.0

The addition of the novocaine makes the injection practically painless. The average dosage is 0.5 cc.

The succinimide is one of the most popular of the soluble salts of mercury for intramuscular injection in the treatment of syphilis. It is readily soluble in water and is procurable in convenient tablet form of 0.013 Gm. (1/5 grain) from the various pharmaceutical houses. The usual dose is one tablet, but this may be increased as needed.

The salicylate, which is the only one of the insoluble salts of mercury used at all extensively at the present time, is usually administered suspended in an oily base. Th dosage of this preparation is usually 0.065 Gm. (1 grain).

Intramuscular Injections

The technic of administration is the same, whether the soluble or the insoluble preparations are employed. An all-glass syringe is much to be preferred, and either a gold, a platinum-iridium or a stainless steel needle is desirable, as ordinary steel needles are amalgamated by the mercury. The needle should be sharp, as there is much less pain when a sharp needle is used than accompanies the use of a dull one. The size of the needle should not exceed 20-gage, and for the soluble mercury salts in watery solution a much smaller needle may be used. The length should be about 5 cm. (2 inches), and longer for very fleshy individuals.

If the syringe is used for nothing but the hypodermic injections in the treatment of syphilis and the same mercurial preparation is employed, it is not necessary to sterilize it between injections, if it is kept where it will be free from dust. The needle, however, should be sterilized before and after each injection.

The site of injection is usually the buttock, although the pectoral, the deltoid, or the muscles of the interscapular region may be employed. The injections are to be given on alternate sides of the body, and about 2 cm. should separate the injections on the same side.

It is imperative to avoid piercing important structures, so the actual site of injections should be chosen with care. Galliot's rule is the simplest guide for injections in the buttock. A line is drawn vertically at the junction of the inner and middle thirds of the buttock, while another line is drawn horizontally two finger-breadths above the top of the great trochanter. The intersection of the two lines and points above and to the outer side of it may be used with impunity.

The injections should be made with the patient lying on a table, face downward with the arms hanging over the sides of the table, and the patient instructed to relax as much as possible. The site of injection is painted with iodine or rubbed briskly with a piece of cotton soaked in alcohol, and the needle, attached to an empty syringe, is plunged directly into the muscle with a swift stroke.

When the needle is in position, the plunger of the syringe is withdrawn slightly to ascertain if a blood vessel has been pierced. If such is the case blood will appear in the syringe and the needle should be withdrawn and a new site selected. If no blood is seen the empty syringe is detached, the one containing the mercurial is attached, and the injection made slowly. The syringe is then detached, the plunger withdrawn slightly, the syringe again attached and a small quantity of air injected. This is for the purpose of forcing all of the mercury from the needle as well as to help distribute the mercury in the tissues. The needle is then withdrawn with a swift jerk and the site of injection massaged gently for a minute or two, which assists in the distribution of the mercury and renders the pain less severe. Usually no dressing is necessary, although a drop of collodion or a small piece of adhessive plaster may be applied. If the latter is used the patient should be instructed to remove it within a few hours.

The intravenous injection of mercury in the treatment of syphilis was first practiced by Bacelli, in 1893, and has been used more or less extensively since that time. The bichloride, the cyanide, the benzoate and the biniodide have been employed. The main objection to the intravenous injection of mercury has been the great difficulty of preventing phlebitis, which occurs very frequently, even to the extent of obliterating the vein. Recently a number of attempts have been made to produce a salt of mercury which could be administered intravenously without the danger of producing phlebitis. Flumerin, which is the disodium salt of hydromercurifluorescein, has proven the most satisfactory of these drugs in my hands.

The technic of the intravenous injection of mercury is practically the same as that of other intravenous injections, and will be fully described in the discussion of the arsenicals.

Arsenic

Herzfeld states that, according to Harles, the use of arsenic in the treatment of syphilis dates as far back as the time of Fallopius and Libavius, and that in the middle of the eighteenth century Hoffman employed the "*flores auri pigmenti diaphoretici*" in the treatment of "*lues venerea inveterata*", in cases which resisted mercurial treatment and also in cases in which ptyalism and mercurial poisoning developed.

Herzfeld further quotes Ziegenbuehler as having successfully used arsenic internally for the treatment of syphilitic arthritis in 1809; while Horn and Renner are said to have employed white arsenic with success in old, inveterate syphilitic lesions.

However, it was not until the pre-arsphenamine days that arsenic was used to any great extent, but about this time numerous investigators reported on the use of various organic compounds of arsenic in the treatment of syphilis. Of these, atoxyl and sodium cacodylate were probably the most popular, and no less great a man then John B. Murphy lent his name to the use of sodium cacodylate, and even as late as 1914 stated that he preferred it to arsphenamine in the treatment of syphilis.

When these organic compounds of arsenic were at the height of their exploitation, Ehrlich stepped upon the stage with his "606", and all other arsenicals were forced into the background. Probably no other therapeutic agent in all the history of medicine created such a furore as did the introduction of this arsenical compound, and, in spite of the fact that Ehrlich's dream of a "*therapia magna sterilisans*" was not

realized, salvarsan, or arsphenamine and its related compounds have proven to be the most valuable drugs of all time.

When salvarsan was first introduced it was administerel either subcutaneously or intramuscularly, and sometimes the reactions from it were very unsatisfactory to the patient, to say the least. These reactions varied all the way from slight soreness, with induration, to intense pain, controlled only by morphine, necrosis and abscess formation.

Mainly on account of these reactions, the subcutaneous and intramuscular routes were soon abandoned for the intravenous and since that time this has been the method employed in practically all cases.

Preparation of Arsphenamine

The original salvarsan or arsphenamine (diamino-dihydroxy arsenobenzene dihydrochloride), is strongly acid in solution, and it is therefore necessary to neutralize it before injection. The following table gives the amounts of a 15-percent solution of sodium hydroxide required to neutralize the various doses:

Arsphenamine				15 percent Sodium Hydroxide				
0.1	gram	requires	approx.	0.19	cc.	approx.	4	drops
0.2	"	"	"	0.38	"	"	8	"
0.3	"	"	"	0.57	"	"	12	"
0.4	"	"	"	0.76	"	"	16	"
0.5	"	"	"	0.95	"	"	20	"
0.6	"	"	"	1.14	"	"	24	"

Before use, the ampule containing the arsphenamine is immersed in alcohol and allowed to stand in it for at least ten minutes. It is then taken out and dried with a piece of sterile gauze and the neck of the ampule is scratched with a file and broken off. About 20 or 30 cc. of sterile, freshly-distilled water are placed in a wide-mouthed flask of 200 cc. capacity, and the arsphenamine is "dusted" on the surface of the water. With as little agitation as possible the arsphenamine is dissolved.

To the solution, which, should be free from gelatinous particles and absolutely clear, is added the sodium hydroxide solution, according to the above table. A precipitate is formed which should immediately redissolve upon agitation. If not clear, more NaOH should be added, drop by drop, until it becomes so. To this solution is added a sufficient quantity of 0.5-percent, sterile saline solution, prepared from chemically pure sodium chloride and freshly distilled water, to make 20 cc. for each 0.1 Gram of arsphenamine used. The solution is then filtered through sterile gauze, after which it is ready for injection.

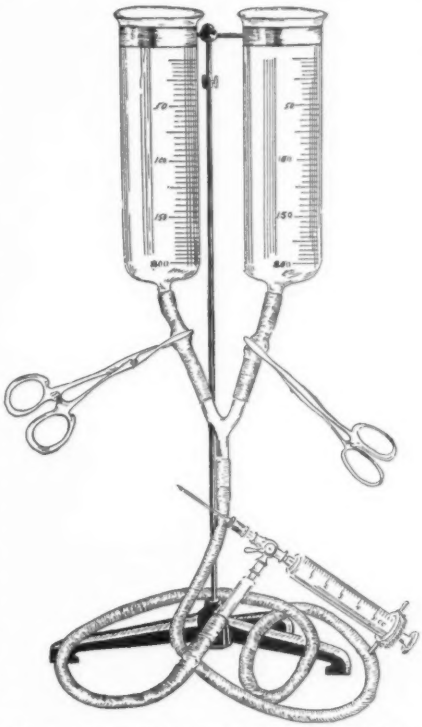

Fig. 1.—Apparatus for giving Intravenous Injections.

Numerous types of apparatus have been proposed for the injection of arsphenamine. Some workers prefer to use a large glass syringe and not dilute the drug so much as outlined above, but this method is not recommended. In the first place the technic of injection is more difficult when a large syringe has to be handled. Then, too, there is more danger of reaction and more danger of inducing phlebitis when concentrated solutions are used.

Intravenous Injections

The following is a description of the apparatus (Fig. 1) which I have devised, and which has proven most satisfactory in my hands:

To each of two graduated glass cylinders of 200 cc. capacity, suspended in a suitable stand or rack, is attached about 6 inches of rubber tubing'. The two upper

arms of a glass Y are then attached to the lower ends of the rubber tubing, and to the other arm of the Y is attached about 24 inches more of rubber tubing. To the distal end of this tubing is attached a glass "window", ground on one end to fit a Luer needle, which in turn is attached to a small, special, metal three-way cock. This three-way cock is made with a Luer socket on the left side for the glass window, and a similar one on the proximal end for a Luer syringe, while the distal end is made to fit a Luer needle.

When ready for use, the arsphenamine is placed in one of the glass cylinders, and isotonic saline solution in the other one. All of the air is forced out of the tubing, and artery forceps are placed on the small pieces of rubber tubing to keep the two solutions from mixing.

The patient lies on an operating table and extends the arm on an arm rest. The flexor region of the elbow is painted with iodine or rubbed thoroughly with alcohol, a tourniquet placed around the arm and the patient is told to open and close the hand a few times, which usually will cause the veins to stand out so prominently that they may be seen or at least palpated. Brisk rubbing of the forearm, in the direction of the elbow, or snapping the vein with the finger will help to make the vein more prominent.

One secret of success in venipuncture is that the needle be very sharp. It should have a comparatively short bevel, although not too short, and for most cases a 19-gage needle is most satisfactory.

When the vein is seen to stand out prominently or is palpated, the syringe, with the three way cock turned so that the connection is between the needle and the syringe, is grasped in the right hand and the skin over the vein is drawn taut with the left hand. The needle is then inserted into the vein, not with a quick jerk, but with a steady push, at an angle of about ten degrees and in the direction of the blood stream. A successful venipuncture is indicated by the appearance of blood in the syringe. If it is desired to collect a specimen of blood it may be done now, and this is one of the advantages of the apparatus.

The turniquet is then removed, the three-way cock is turned so that the connection is between the glass window and the needle, and the artery forceps is removed from the tubing connected with the saline solution. If the point of the needle is free in the lumen of the vein the saline will run freely. The artery forceps is then replaced, cutting off the saline, and the other removed, allowing the arsphenamine to run. When this has run down to the glass Y, the two artery forceps are a g a i n changed and a sufficient amount of saline solution to "chase" the arsphenamine out of the rubber tubing is allowed to run. When this has been accomplished, the three-way cock is turned to "neutral" and the needle removed. A piece of sterile cotton is placed over the needle just before it is removed and pressed down on the puncture hole and the arm held up above the head. In three or four minutes the cotton is removed and a drop of collodion or a small piece of adhesive plaster applied.

The advantages of this apparatus, in addition to the ease with which a specimen of blood may be collected if desired, as mentioned above, are that one person can operate it himself very satisfactorily, there is absolutely no danger of any of the arsphenamine escaping into the tissues and no blood is spilled.

Neoarsphenamine

The great difficulty encountered by many workers in preparing arsphenamine for injection led Ehrlich to seek a substance of equal potency but requiring a less complicated technic in preparation. On his 914th experiment this was found, was designated "914" and, owing to its resemblence to the original preparation, the new one was termed neosalvarsan.

Neosalvarsan or neoarsphenamine is much more soluble in water than is the older preparation, its aqueous solution being of a yellow color of a depth depending upon its concentration, and of neutral reaction and therefore it does not need to be neutralized. Its method of injection is the same as that of arsphenamine, although it may be given in concentrated solution with more impunity than can the older preparation.

Silver Arsphenamine

Silver arsphenamine was introduced into the therapy of syphilis early in 1918, by Kolle, the successor of Ehrlich. It is a complex combination of the disodium salt of dioxy-diamino-arsenobenzol with s i l v e r oxide. It is a brownish-black powder, readily soluble in cold water, and requires no neutralization.

The dosage of silver arsphenamine is smaller then that of either the original arsphenamine or neoarsphenamine, the maximum dose being 0.3 Gram. It is well, however, to begin the treatment of a patient with 0.1 Gram and increase the dose if it is well tolerated.

Silver arsphenamine is particularly indicated in neurosyphilis, and is injected in the same manner as arsphenamine.

Tryparsamide

Tryparasamide, which is N-phenyl-glycinamid-para-arsonic acid, was prepared by Jacobs and Heidleberger in the Rockefeller Institute, and after a very thorough clinical trial was placed upon the general market in January, 1925. This preparation contains 24.57 percent of arsenic, and as the dosage is from 1 to 4 grams it is seen that each dose contains the enormous amount of 245 to 737 milligrams of arsenic.

Tryparsamide is a white crystalline powder which is readily soluble in cold distilled water, and is prepared and injected in a manner similar to neoarsphenamine. It is of comparatively little value in the treatment of syphilis, other than that of the central nervous system, and is of particular value in paresis. It, however, should be used only in selected cases, and each case should be examined carefully by a competent ophthalmologist, both before and after each treatment, for evidences of optic atrophy.

Bismuth

Sazerac and Leviditi and Fournier and Guénot reported on the use of bismuth in the treatment of syphilis in 1922, although, according to the first named authors, Sauton and Robert were the first to use this metal in the treatment of spirochetosis of fowls. They used the sodium-potassium-tartrobismuthate, and this salt, on account of its low toxicity, has been used most extensively in human beings. However, quite a number of other salts of bismuth have been used. Among these may be mentioned phenyl-formitate of bismuth, bismuth-sodium-tartrate, bismuth salicylate and sodium-bismuth-thio-glycollate.

Some of these salts are quite painful when injected intramuscularly in aqueous solution, but are comparatively free from pain-producing properties in oily suspensions. This is particularly true of the sodium-potassium-tartrobismuthate and the bismuth salicylate. The former is also prepared in a glucose-aqueous solution which is nearly painless. Sodium-bismuth-thio-glycollate may be administered intramuscularly in aqueous solution without pain, and may also be administered intravenously.

The technic of intramuscular injection of bismuth is the same as for the intramuscular injection of mercury, and has been fully described above.

Sodium-bismuth-thio-glycollate as stated above, may be injected intravenously. The technic is simple. A 2-cc. glass syringe is filled with sterile distilled water and the contents emptied into the ampule containing the bismuth, after the neck has been filed and broken off. The bismuth, which is a yellow powder, goes into solution readily, and is then drawn up into the syringe. A 22- or 24-gage needle is used and the injection is made in a manner similar to the injection of arsphenamine. The average dose of the bismuth salts is 0.065 Gm. (1 grain), although larger doses may be given.

Sodium Iodide

While the iodides are not, strictly speaking, specifics for syphilis they are used extensively in certain types of this disease. Both the potassium and the sodium iodide have been used for intravenous injection, but the latter is the more satisfactory for this purpose. A solution of from 5 to 10 percent, in distilled water, which may be sterilized by boiling, is recommended, and the injections may be made either with a large glass syringe or with the apparatus described for the injection of arsphenamine. The dose is usually 1 to 2 Grams, but the enormous dose of 22.5 grams was injected by Howard.

1.—Rubber tubing for use in intravenous therapy should be as nearly "pure gum" as possible, black in color and, before using it the first time, should be soaked over night in a 5-percent sodium hydroxide solution. Care should be taken that the lumen of the tube is filled with the solution.

Progress In the Chemotherapy of Malaria

By William E. Deeks, M.D., *New York City*
General Manager, Medical Department, United Fruit Co.

AFTER 1638, when the Countess of Chinchon, wife of the then Governor of Peru, was cured of a fever by quinine, the use of this alkaloid rapidly extended over the known world and became established as a specific for "fever and ague"; more especially, in later days, for malaria.

Quinine is one of the few drugs the empiric use of which in therapeutics has been confirmed by scientific research. It seems fitting, therefore, that in this number of Clinical Medicine and Surgery, devoted specially to Chemotherapy, quinine —or its derivatives—as one of the oldest and best established chemical drugs, should receive due recognition; and more so because, quite recently, new and important developments have arisen in the chemotherapy of malaria by quinine and its derivative, *Plasmochin*.

Malaria, particularly of the estivo-autumnal type, has always been one of the most important diseases in tropical and semi-tropical regions. Its heavy incidence has been a strong barrier to the industrial development of tropical countries and its contol is a matter of supreme importance to corporations, such as the United Fruit Co., operating in these regions, as it has been found that, in some labor camps in the tropics, malaria accounts for about 90 percent of all the sickness.

The Control of Malaria

The most important therapeutic consideration in the control of malaria is the prevention of relapses or recurrences following treatment, and the value of any remedial agent is in direct proportion to its ability to effect this end. It is now well understood that the infection of mosquitoes (and the consequent spreading of the disease) occurs only when the malarial subjects are carriers of gametocytes (crescents) in the peripheral blood. The numbers of such potential mosquito-infectors in a malarial population is relatively small, being roughly about one-fifth of the malarial population, as found by investigation.

While quinine is a specific against the schizonts of all types of malaria (which alone are responsible for the clinical symptoms) and is the drug of election for the rapid abatement of such symptoms in acute cases, yet for some unknown reason it has been found that quinine administration in such acute cases favors the increase of gametocytes in the peripheral blood and that these sexual forms of the parasite are prone to persist in the peripheral blood for a long time. In 1926, Dr. H. C. Clark, Director of Laboratories of the United Fruit Co., found that 45.9 percent of the treated malarial patients left the hospitals still positive for parasites, usually gametes (crescents). It is therefore evident how great a menace such gamete carriers are in the spreading of malaria. The draining of swamps and other breeding grounds, and the campaign methods directed against the mosquito, are of only secondary importance compared with the problem of the heavily gamete-infected carrier.

While quinine has been more effective than any other known agent against the clinical symptoms of malaria, it has become apparent from investigation that it affects only the symptom-creating, asexual forms of the malarial parasite; hence it has become necessary to search for some agent capable of a similar action on the sexual types—the gametocytes—in the peripheral blood. The finding of such an agent would mean pactically the solution of the malaria problem and the eradication of malaria, inasmuch as its administration would prevent the infection of mosquitoes. It has, therefore, been deemed an important problem for the United Fruit Co.'s Medical Dept. to find such an agent, if possible.

Plasmochin*

Plasmochin, a derivative of the quinolin nucleus, synthetically built up on the principles of modern chemotherapy, has been found an excellent substance for the result

*Plasmochin was developed, and is manufactured, by the I. G. Farbenindustrie Antiengesellschaft, in Leverkusen, Germany.

required; and, in association with quinine, gives a curative treatment for malaria which has been found, after extensive trials, to approximate the ideal.

The paramount value of Plasmochin rests in its effectiveness in ridding the peripheral blood of gametocytes, thus rendering the treated individuals non-infective to mosquitoes. In many hundreds of cases, treated in the United Fruit Co.'s Hospitals and labor camps, in which, prior to treatment, a large proportion of the patients were known to be heavy carriers of gametocytes, these disappeared from the peripheral blood from the fourth to the fifth day following Plasmochin administration. Thus, in one camp, 104 out of 500 malarial patients were found to be gametocyte carriers. In none of these 104 patients could gametocytes be found on the fifth day following Plasmochin treatment. Very rarely do crescents persist in the peripheral blood up to ten days following this treatment. On the other hand, Plasmochin has apparently little or no effect on the schizonts of estivo-autumnal malaria.

The value of Plasmochin in the destruction of crescents, as compared with quinine, can easily be estimated from the following observation made at one of the labor camps:

Of 36 cases (35 being estivo-autumnal), treated with quinine alone and discharged from the hospital after 7 days, 20 showed crescents at the time of discharge and 3 more showed abundant crescents. Of 31 similar cases (27 being estivo-autumnal), treated with quinine *and Plasmochin*, 3 only showed some crescents at the time of d i s c h a r g e from the hospital and none showed abundant crescents.

Plasmochin is mainly effective against gametocytes; but while its action on the schizonts of the estivo-autumnal types is negligible, it apparently is active in clearing schizonts of the tertian and quartan types of malaria from the peripheral blood.

Combined with quinine, the results are, in general, the clearing from the peripheral blood of both the schizonts and gametocytes of malaria.

Toxicity of Plasmochin

If given in too large a dosage, or over too prolonged a period of time, Plasmochin may cause toxic symptoms. Some patients apparently have an idiosyncrasy to this drug. A divided, daily dosage of 80 mgm., or even 40 mgm., in a few cases may exceptionally cause prostration, cyanosis, somnolence, epigastric distress, and jaundice (with other symptoms of some blood cell destruction). In 250 patients, treated by Plasmochin in one camp, there were 6 serious toxic reactions; and 6 also in a series of 500 in another camp. The simultaneous administration of Plasmochin and quinine appears greatly to lessen the toxic tendency of the former.

Fortunately the effective action of Plasmochin on the gametocytes falls well below the limits of the amounts necessary to produce toxic symptoms.

Plasmochin without quinine does not prevent relapse nor the development of blackwater fever.

Dosage

Excellent results are obtained in all types of malaria after the administration of 0.03 to 0.06 Gm. (½ to 1 grain) daily (.01 to .02 Gm. t.i.d.) of Plasmochin, together with 20 to 30 grains (1.33 to 2.0 Gm.) of quinine, continued for 5 or 6 days. The dosage of quinine may be increased in very acute cases. Three or four days subsequent to the completion of this course of treatment the blood should be examined and, if parasites persist, the treatment should be resumed.

The results obtained in different camps with Plasmochin-quinine treatment were uniformly excellent—so much so that one of the investigators reported: "The failure of certain gametocyte carriers, apparently excellent infectors, to infect mosquitoes after a short Plasmochin-quinine treatment was so striking that we undertook further tests of the viability of gametocytes not yet eliminated from the blood of treated carriers." These tests apparently showed that the gametocytes are so crippled that they are rendered incapable of forming healthy oöcysts.

A certain discretion should be observed in the method of administration, owing to the possible toxic effects of Plasmochin. In ambulatory cases, not under daily supervision by a physician, the daily dosage of this drug should not exceed .04 Gm., in combination with 1 to 2 Gm. of quinine, for a period not to exceed 6 days; or .06 Gm. of Plasmochin, with the same dosage of quinine, over a period not to exceed 4 days. Whenever possible, all cases so treated should return for a re-examination within from 3 to 4 days after the course

is completed; and if the blood is still positive, the course of treatment should be repeated.

All ambulatory patients should be warned that, if they experience headaches, dizziness or gastric distress, or if blueness developes in the face or lips, the drug should be immediately suspended and that they should report to the physician for further instructions.

In conclusion, extensive clinical investigations, with all types of malarial cases, shows that Plasmochin, associated with quinine, provides a chemotherapy of malaria which bids fair, so far as the indications point, greatly to decrease the incidence of this disease, if not entirely to eradicate it, in time.

17 Battery Place.

Calcium Retention in Acidosis*

(A Preliminary Report)

By Prof. Dr. Adolf Bickel, *Berlin, Germany*

AS *I HAVE* in mind to conduct an extensive series of experiments on the influence of calcium upon oxidation processes, it seemed to me an essential that proper attention should be paid to the question of calcium retention. With this in mind I have first compared the action of calcium lactate with that of the double lactate of calcium and sodium, to which an action promoting calcium retention is ascribed as a result of its sodium lactate component.

It was first necessary to determine what influence these preparations would have upon an animal kept for some time upon a diet leading to acidosis and a consequent increased loss of calcium in the urine. The calcium-sodium lactate corresponds to a preparation, **Kalzan**, which is found on the market at present, and contains in each tablet 0.5 G. of this double salt.

The dose of calcium lactate alone yields a smaller addition of alkali to the body than does the dose of Kalzan, provided that the amounts of calcium introduced into the body by means of calcium-sodium lactate and calcium lactate are approximately the same. In order to establish this, I have had tablets prepared, each of which contains 0.015 G. of calcium. Two tablets of calcium lactate correspond to 1 tablet of the double salt, which contains 0.03 G. of Ca.

One can produce a general disturbance of metabolism in young rabbits, as a result of which a progressive loss of calcium through the kidneys occurs, by a one-sided diet of dry oats with the addition of water. The bodies of these animals gradually become impoverished in calcium.

The further arrangements for the experiments were then established. Two young male rabbits of the same litter and approximately of the same weight, which were in the period of growth, were placed upon the above-mentioned oat diet and the calcium content of the 24 hour amounts of urine estimated. In a five-day preliminary period the animals obtained no sort of calcium addition to their feed. In the following four-day test period the animals obtained their addition of calcium; Rabbit I, 0.03 G. Ca. daily, in the form of one tablet of calcium-sodium lactate, and Rabbit II, 0.03 G. Ca. in the form of two tablets of calcium lactate. Following this test period, came a six-day final period, in which the animals were again placed on the original diet without addition of calcium*.

While animal I, in the preliminary and test periods, consumed on the average almost the same amount of oats (84 and 86 G.) and showed first, in the final period, a lessened intake of food (50 G.); in the case of rabbit II, the intake of oats fell, in the test period, from the value of the preliminary period (73 G.) to 55 G., and sank still further (to 43 G.) in the final period. Notwithstanding these relations in the intake of food, both animals showed an increase in body weight in the test period; in the case of animal I, about 97 G., and in animal II, about 44 G. In the final period animal I increased still further

*From the Experimental-Biological Department, Pathological Institute of the University of Berlin.

*Protocols of these experiments, which accompanied the article, have been omitted for lack of space.—Ed.

(about 16 G.), while animal II lost about 27 G. in weight.

On account of the lessened intake of food in the test period, animal II received, with the oats, absolutely less calcium than in the preliminary period, and especially if this be calculated on the basis of the increased weight in this period, even though the calcium of the oats is very small in amount. It had, in the preliminary period, 67.20 G. per kilogram of weight; in the test period, 40.13 G.; and in the final period, 38.63 G. of oats; while rabbit I took in daily, per kilo of weight, 64.96 G. of oats in the preliminary period; 61.64 G. in the test period; and 35.90 G. in the final period.

By calculating on the basis of 1 kilo of body weight, rabbit II, therefore, received, with the oats, approximately the same amount of Ca. in the preliminary period as rabbit I (67 G., as against 65 G. of oats); however, in the test period, rabbit II received considerably less calcium with the oats—approximately 2/3 of the amount—than rabbit I took with its oats (40 against 61 G. of oats); while in the final period the calcium addition from the oats was about the same with both rabbit II and rabbit I (38 G. against 36 G. of oats).

In the test period, in which rabbit II received only about 2/3 of the calcium amount referable to the oats as rabbit I received, and in which period both rabbits received the daily addition to their feed of 0.03 G. of Ca. rabbit II was placed in a worse position, at least as regards the oral addition of calcium, than was rabbit I; however, rabbit II showed a urinary excretion of Ca. per kilo of body weight, of 13.09 mg., while rabbit I showed only 7.14 mg. per kilo of body weight. In other words, the renal loss of calcium by the rabbit which was a little worse off with reference to the oral intake of calcium, was almost 90 percent greater than in the case of the other. Provided the daily addition of calcium, to the amount of 0.03 G., to the food is absorbed in the same way by both animals, as would be assumed from the identity of the calcium compounds in both preparations, more calcium must have been retained by animal I, which received the double salt, than by animal II, which had the calcium lactate pure.

Also, in the final period, the peculiar action of each of these calcium preparations comes clearly in view. In the case of rabbit I, the Kalzan animal, the calcium excretion returned almost to the value of the preliminary period; while with rabbit II this calcium excretion remained in the final period, almost 100 percent higher than in the preliminary period.

From all this it follows that calcium-sodium lactate assures a far better retention of calcium, after peroral introduction into the system, than is brought about by corresponding doses of calcium lactate.

The theoretical explanation of these experimental results must proceed from the point of view that a change in the mineral metabolism is brought about through the feeding of oats alone to young rabbits, which metabolic disturbance especially favors the appearance of an acidotic state; and, entirely aside from this, a disturbance in the vitamine utilization of the body is brought about, which, however, should have no striking connection with the causation of a disturbance in calcium metabolism, especially in view of such brief experiments as we have outlined here.

In this acidotic state, with its marked calcium mobilization and calcium excretion, the high alkali content which the double salt has, in distinction from calcium lactate, compensates for the acidotic disturbance and indirectly reestablishes especially favorable conditions for calcium retention.

From all this it follows that, in such metabolic disturbances as are here experimentally shown in rabbits through feeding with oats alone and, naturally, in similar general pathologic metabolic disturbances, calcium-sodium lactate is superior to pure calcium lactate for the establishment of a normal calcium balance and calcium retention.

It may be further mentioned that in a fourth experimental period, which followed immediately after the final period of the former series and in which rabbit I, which previously received the double salt, was now given calcium lactate; while rabbit II, which before had received calcium lactate, was now fed with Kalzan, the calcium elimination through the urine sank appreciably in the case of the present calcium-sodium rabbit; while in the case of the present calcium lactate rabbit, the urinary calcium output increased.

It is seen therefore, that the double-salt, as opposed to calcium lactate, always promotes calcium retention.

The Nature of Malignant Tumors and the Criteria of Cure in Relation to Chemotherapy

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FEW diseases have engaged more attention, from the standpoint of experimental chemotherapy, than have malignant tumors. While the pathogenesis of cancer and sarcoma is still unknown, specific therapeutic measures of this kind have been undertaken on the assumption that the cancer cell is different from the normal cell from which it originated, and that certain substances will show a selective affinity for them; in other words, that specificity may be present among organotropic substances. Here, of course, the difficulties are great, because the structural, biologic, and functional differences between the normal cell and the cancer cell may be slight, and substances must be found that possess a high affinity for the cancer cell only.

With the discovery of inoculable carcinomas and sarcomas of mice and rats, whereby these tumors could be reproduced at will on a large scale in these animals, it was but natural that early and persistent attempts were made to discover chemical agents, and particularly dyes, possessing a special affinity for tumor tissues along the lines and principles of vital staining.

The earliest investigations in the chemotherapy of experimental cancer and sarcoma were based primarily upon the assumption that these growths were caused by some form of parasite. The ease with which some cancers and sarcomas of mice and rats are transferable from animal to animal through an indefinite number of generations, along with the evidences of acquired immunity, have long given support to various theories of parasitism, and *while many different protozoa and bacteria have been described as causing cancer, none has been proven or accepted as the etiologic agent.* Gye[1], working with the Rous chicken sarcoma, has recently claimed that a specific virus is the cause of malignant disease but that it is ineffective until a second substance, obtained from tumor cells and called "specific factor", breaks down the cell defenses and thereby enables the virus to infect and produce the disease. But Harkins, Schamberg, Kast and myself[2], Harkins and myself[3] and others have been unable to confirm this work.

It may be that parasites and their toxins are capable of stimulating epithelial and connective tissue cells into lawless states of proliferative activity, but it is certain that various non-parasitic chemical agents are capable of producing these effects, with the production of cancers and sarcomas. In other words, the parasitic nature of cancer and its contagiousness have never been proven, although precancerous conditions may be directly or indirectly transmissible and explain socalled cancer outbreaks, "cancer houses", "cancer cages", etc. Indeed, of far greater importance than researches on the parasite of cancer is the study of precancerous conditions and diseases, which, as has been frequently observed, often result in cancer.

Experimental Cancers

At the present time most interest is being placed in the results of experiments showing that prolonged irritation of cells may result in the production or elaboration of substances greatly stimulating cell proliferation and that malignant growths produce continuously, of their own accord, growth-stimulating substances which normal tissues elaborate only in response to cell damage. It may be that the growth-stimulating substance, obtained for example from tumor extracts, is in the nature of a parasite substance, but this is not at all likely and at least is definitely known to be furnished by the prolonged irritation of cells by tar, paraffin and other chemical substances.

As shown by Deelman[4], Murray[5] and others, it requires the prolonged applica-

tion of tar before malignant proliferation results, and this harmonizes perfectly with the chronic character of the irritations that are usually necessary to produce cancer in man. In mice, the tar cancer is not produced in less than three months, usually from six to nine months being required, which is a large proportion of the span of life of these animals; and even eighteen months of bi-weekly application of tar may fail to induce cancer formation, showing that there is a marked difference in resistance or susceptibility of different mice to the production of malignant growths. It would seem highly probable, in view of what has been shown concerning the influence of heredity on the spontaneous occurrence of tumors in mice, especially by Loeb and Slye, that this factor accounts for the difference in behavior of different mice under the same stimulus to cancer formation.

In addition to tar, other agents have been shown capable of producing cancer in animals. All these are of an irritating nature, being foreign to the cells of the body, and provoking in them the response of proliferation and increased cellular activity.

Evidence derived from experiments has not only brought support to the doctrine that cancer follows chronic irritation, but has also very considerably narrowed the issues by demonstrating that certain irritants are very potent agents in producing tumors, whereas others have not been found to possess carcinogenic properties—the term Leitch[8] has devised. Thus Murray[7] conducted experiments in which unaltered tar, alcoholic extract, and ethereal extract of tar were applied to separate areas of the dorsal skin of each of sixty normal mice. After four months, when the first tumor appeared, fifty mice survived, and of these twenty-five presented malignant new growths. Twenty-two animals bore carcinoma at the site painted with the ethereal extract; twelve had carcinoma at the site treated with the original tar; and two only had carcinoma at the site treated with the alcoholic extract. In one of these animals no tumors appeared at the sites treated with the apparently much more efficacious whole tar and ether extract.

By the frequent application of crude shale oils containing paraffins, Leitch[8] has produced tumor formations in thirty out of seventy-four mice which survived the treatment for more than 100 days. Owing to the increasing death rate after that time it is impossible to say how many more would have developed tumors had they lived long enough, or how many of the simple tumors produced would have gone on to malignancy. One animal resisted for more than nine months. The disappearance of some of the simple papillomas corresponds with what is found in man. In many of the older papillomas, considerable difficulty has been encountered in forming a judgment of their benignity or malignancy. Experimental evidence shows that it takes at least ten years of exposure to paraffin oils to produce cancer in man—which corresponds to actual experience.

In the hope of determining experimentally whether arsenic might act as a tumor-producing or carcinogenic agent, Leitch and Kenneway[9] fed a series of rats and mice on bread containing arsenic. The experiments were unsuccessful. Then potassium arsenite was applied locally. In three months' time, two-thirds of the mice had died, but a growing tumor was produced in one of the survivors. Microscopic examination of a section through the tumor showed it to be typical squamous cell carcinoma. There were also metastases in the lung in this animal. Cancer has also been produced experimentally by Passey[10] by means of soot mixed with quicklime. In animals fed a fat-soluble-vitamine-poor diet, the tumors appeared a little earlier.

The irritant is, therefore, in a sense specific; it invokes a response in the cells, which is at first similar to that aroused by other stimuli, but later, on account of its peculiar nature, leads to the anarchic and progressive proliferation termed cancer. The evidence is that certain irritants easily produce cancer, while others do not. A second fact which these experimental studies of cancer have brought to light is that the specific irritant produces cancer only in certain animals, and only in the susceptible tissues of these animals.

Another important fact made clear by these experimental studies is that a considerable space of time may elapse between the action of the irritant and the appearanc of the neoplasm as mentioned above. A careful study of human cancer has often failed to reveal any recent antecedent irritation, but sufficient consideration has not been given to the possibility that a bias toward malignancy may be imparted to cells by some previous, and even long previous, irritation. Experiment has shown that cancer is not essentially a disease of

ageing tissue; the reason why it occurs more frequently with advancing years is capable of another explanation than that the cells are manifesting senile changes. The essential point may be the length of time the casual agent is in operation. Since, in most instances, this requires a protracted period, it becomes obvious why cancer is usually a disease of middle or old age.

To the pathologist it is of great interest that, after the application of paraffin oil to mice, in some cases carcinoma and in other cases sarcoma developed in approximately the same time as previously mentioned. Thus, two very different kinds of tumor can be produced by the same agent, according to whether the irritant substance affects chiefly the epithelial or connective tissue cells. All that is claimed for these tumor-producing agents is that they bring about a pathologic state of the tissues, and that on this prepared soil the undetermined causal agent of cancer can then exert its action, as shown by Leitch[11]. When tar has been applied repeatedly for a certain length of time and the irritant is then removed tumors, even carcinomas, may make their appearance at a later date. It must be that the irritation produces in the normal cells subjected to its influence some profound *metabolic* change, undetectable by the microscope, so that they eventually proliferate in an unrestrained and in a harmful fashion. Leitch believes that it may be concluded that the neoplastic response to an irritant is a slow tissue reaction that exhibits no defensive property and that subserves no useful function.

The fact that after a tar epithelioma has been extirpated from a mouse, subsequent applications of tar do not induce a further tumor is an observation which may prove to be of great practical importance since it suggests that the occurrence of one form of cancer in an individual protects the body in some way against the occurrence of another. Thus Murray found that after a rat cancer has begun to grow, subsequent application of tar at another point usually fails to produce a new focus of cancer development. Similar negative results of tar painting in animals from which primary spontaneous mammary gland tumors had been removed by operation support the hypothesis that the presence in an animal of a cancer has some systemic influence that inhibits cancer formation elsewhere. As yet, the number of experiments on this point are too few to establish positively so important a matter as this, especially in view of the contradictory fact that multiple primary spontaneous tumors are remarkably common in laboratory mice, and by no means extremely rare in man. But at least the numerous new facts and suggestions brought forward serve to emphasize the great possibilities the new methods of cancer investigation have for adding rapidly to our understanding of the underlying principles of cancer pathogenesis.

The Nature of Malignant Tissues

Again, as with human cancer production, excessive injury to the tissues is less likely to lead to cancer formation that a milder stimulation without destruction; for example, roentgen-ray and radium burns are less likely to be the site of cancer than areas of milder but protracted irritation. Sometimes a combination of tissue traumatism with the stimulation of cell growth by tar has been found to accelerate the production of the neoplasm. This fact is particularly important in view of the observation of Drew[12] on the behavior of tissue cultures of normal and cancer cells. It has been known by investigators in this field that tumor cells inhibit the peculiarity, shown by embryonic tissues, of being able to begin to proliferate almost immediately when placed in a suitable culture medium; whereas quiescent adult tissue cells do not begin to grow until after a comparatively prolonged interval. Furthermore, when to such adult cells in cultures is added the extract of slightly autolized normal tissues, they show a speed of growth similar to that of tumor cells. Extracts made at 0°C., that is, without autolysis, have no such stimulating effect; but Drew found that even cold extracts made from cancer tissue have the same stimulating property as the extracts of autolyzed normal tissues. Murray considers that, from these observations, many times repeated and always with the same result, it is probable that these malignant growths produce continuously, of their own accord, growth-stimulating substances which normal tissues elaborate only in response to cell damage.

A direct relation exists between the growth-stimulating power of the tumor extracts and the rate of growth of the tumor used to prepare it. This suggests strongly that the biochemical mechanism by which their proliferation is maintained is, at any rate in part, by the elaboration of this growth-activating substance or substances.

A certain amount of activating substance is probably produced by any kind of cell damage, and when, by constant repetition, this production has become automatic, proliferation will continue after removal of the cause of protoplasmic disintegration. Temporary hypertrophies would, in this conception, correspond to the purely reactive production of activator, ceasing when the irritant is removed; benign growth to an autonomous production in small amount; and malignant growth to a more abundant production.

Apparently, in cancer formation, the cells acquire the property of producing continuously and in relatively large amounts the same sort of stimulating substance that adult tissues produce or release only when injured and for the purpose of exciting reparative processes. Embryonic tissues, like cancer cells, also produce the growth-stimulating substance. In support of this conception of the pathogenesis of cancer growth is the observation of Deelman previously quoted, that traumatism of the tissues, which might set free growth-promoting substances, hastens the production of tar cancer.

Burrows[13] however, does not accept this view, insofar at least, as it is based upon the results of tissue cultures. In his opinion, "It is evident that the growth of body cells depends always on the accumulation of certain soluble products of their metabolism about them. These substances are formed in the oxidation reaction. Cancer need not be considered a degenerative phenomenon. If one is to give an explanation for cancer from the studies of tissue cultures alone, it must be assumed to be the result of a condition capable of establishing a dense mass of cells having a relatively poor blood supply (conditions suitable for maintaining a certain high concentration of certain blood-soluble oxidation products about the cells). Our studies of coal tar, other lipoid solvents, chronic inflammation, certain congenital tumors, animal parasites, etc., have confirmed this view".

It is evident, however, that the theory just reviewed, indicating that chemical agents, by prolonged irritation, may induce changes in the cells whereby cellular activators are produced, is supported by a great deal of very careful, prolonged and meritorious investigation. Furthermore, it is not improbable, as discussed by Luden[14], that metabolic disturbances may bear a relation to the processes concerned, although it has been shown experimentally that vitamine deficiency, to the point of danger to life, has no inhibitory effect on cancer, and that it is improbable that any single cause or cure for malignant tumors is likely to be discovered. But if it is finally proven and accepted that cancer and sarcoma are due to primary changes in the cells, by which tissue activators are produced by prolonged irritation or, the converse, that substances are produced which neutralize physiologic restraint on cellular proliferation and activity, the question arises, how may chemotherapy influence the mechanism? If the primary changes are due to the effects of parasitic agents (and it is within the realm of possibility that parasitic toxins may act as irritants, just like tar and paraffin), it may be that chemotherapeutic agents may inhibit the production of these substances. But if the irritant, parasitic or chemical, were allowed to act until cells were produced, endowed with the faculty of automatically producing the tissue-stimulating substances and of rapid and riotous proliferation, then chemotherapy or any other therapy, to be successful, must destroy these cells and neutralize or destroy any activator remaining in the tissues to prevent the formation of another generation of malignant cells.

Contrary to prevailing opinions, chemotherapy, therefore, is not without considerable interest in relation to the treatment of malignant tumors, not so much from the standpoint of destruction of the hypothetical parasitic agents of malignancy, but rather in relation to the possibility of the destruction of those cells endowed with unusual faculties for rapid and riotous proliferation, as the result of primary and unknown changes induced by prolonged irritation, by which cellular "activators" are produced or cellular "restrainors" removed.

The Criteria of Cure of Malignant Tumors

It may be well first to establish clearly in our minds what should be the criteria by which cures are to be judged. This is all the more important since, as so well expressed by Weil[15], "The natural course of the disease is associated with such fluctuations that a sanguine therapeutist can gain some encouragement from even the most hopeless cases. Hence it follows that every mode of treatment has found adherents. The market is flooded

with cancer drugs, and cancer charlatans flourish in the most highly educated communities. Unfortunately, even well trained, honest and reputable physicians have fallen victims of this fallacy, and have lent their names to the support of modes of treatment which in reality produce no determinable effect on the natural evolution of the disease". It was the desire to combat this unfortunate tendency which led Weil[16] to attempt to establish the following criteria of therapeutic effect in cancer, which are so well and clearly expressed that I can do no better than quote them *in extenso*:

"In determining the effects of any given mode of treatment on a tumor, a variety of criteria may be relied on. Circulatory changes in the tumor, the relief of pain and the restoration of a secondarily impaired function are certain of the criteria on which stress has been laid by the majority of observers in the past. Important as are these criteria in determining the progress of purely inflammatory processes, it is unquestionable that their value in judging of the effects of therapeutic methods, when applied to malignant disease, is open to criticism.

"It is a curious and interesting fact that almost every therapeutic claim made in recent years in connection with cancer has included among its virtues the relief of pain. This is true of vaccination with cancer tissue, of Hodenpyl's method and of many others. In view of this very general effect, not much stress can be laid on this symptom, and it is probably fair to assume that, in the great majority of these cases, the result is in no small measure psychic.

"The improvement of function is also largely a subjective phenomenon, and as such requires most careful criticism. Osler relates that he has known a patient with gastric cancer to be relieved of digestive disturbances and to gain 18 pounds in weight as the result simply of the visit of a sanguine consultant who denied the presence of a tumor. Improvement in the ability to chew food, to articulate words or to move a limb are phenomena familiar to those who attempt to treat cases of cancer. The victims of this disease seem to be in a very high degree 'suggestible' and impressionable and respond nobly to every therapeutic effort.

"Circulatory changes in tumors offer an interesting group of clinical symptoms. The observation has often been made, especially in ulcerated new growths, that treatment is associated with swelling, peripheral hyperemia, and an altered character of the discharge. In spite of the fact that there is no reasonable relationship between this congeries of symptoms and the actual cure of the tumor, they generally receive considerable emphasis and are cited as an indication of the specific local action of the agent employed. It is also true, however, that the growth may continue to advance in spite of their presence. It is of some importance to inquire into the mechanism which produces these circulatory changes and into their clinical interpretation.

"It is a well-known fact that many drugs when introduced into the body, either by the mouth or through the skin, are excreted, not only by the normal channels of elimination, such as the kidney or the intestine, but also from such ulcerated surfaces as may be present on the body. This is easily shown to be true, for example, of certain of the anilin dyes, which when introduced by way of the veins, produce an intense discoloration of the dressings over ulcers. It is likewise true of certain of the metals, such as arsenic. In order to understand the series of events previously enumerated it is therefore only necessary to assume that the therapeutic agent is excreted from the ulcerated surface of tumors. If an irritant, it will tend to produce hyperemia of the margins of the ulcer, and an increase of the secretions. If an astringent, however, it may produce just the opposite of these effects. Such a result, however striking, is purely accidental, and has no necessary bearing on the growth or destruction of the tumor itself. It constitutes a symptom on which no reliance should be placed.

"Excluding from consideration all of these secondary factors, we may conclude that the observation of the *size of the tumor itself* is the sole criterion on which we can place reliance in judging of the effect of therapeutic measures. This implies, in the first place, that a tumor must be accessible to fairly accurate measurement. Tumors of the uterus, for example, and intra-abdominal growths will only exceptionally fall into this class. In the second place, indirect evidence of a decrease in the size of tumors, such as is afforded by the increased permeability of obstructed passages, as in the case of tumors of the esophagus, pylorus or intestine, must be accepted only with great reserve. Remissions in the obstructive symptoms characteristic of such tumors are a frequent feature of the normal evolution of the clinical history of such growths. The relief of osbtruction, however, may be due either to necrosis of the obstructing portions of the tumor, while the remainder continues to grow progressively, or to a relief of the accompanying muscular spasm. Finally, evidence of decrease afforded by the roentgenogram is not sufficiently exact in most cases to afford ground for so important a conclusion as that at present in question.

"Not only must there be unquestionable evidence, however, of the diminution in size of the tumor, but this diminution must be of a kind not ordinarily attributable to the natural evolution of the tumor. It is safe to say that multiple tumors offer enormous difficulties in the matter of interpreting therapeutic results. At present we have in the wards of the hospital a patient with multiple metastatic carcinomas of the skin. For several months we have at intervals made accurate measurements of certain of these tumors and have found that some have undergone retrogression, others have entirely disappeared, while still others have continued to grow steadily. In the case which afforded the ascitic fluid used in Hodenpyl's experiments, many of the lymphatic metastases underwent complete retrogression, while the metastatic process in the liver, as was demonstrated at necropsy, increased progressively, and ultimately almost destroyed that organ. Thus, in multiple carcinosis, the retrogression of individual nodules is no indication that therapeutic intervention has produced an improvement.

"I shall not delay to emphasize those variations in the size of solid tumors which accompany hemorrhage and its absorption, edematous swelling, necrosis in the depths, and other familiar factors which clinically simulate, or induce, the softening and the reduction that are so often attributed to therapeutic interference. But it is important to draw attention to a similar feature in that type of superficial epithelioma known as rodent ulcer. These new growths not infrequently advance at one point of the periphery, while they recede at another, and thus cicatrization and contracture may simulate a partial recovery. This effect is due in part to alterations, not in the growth itself, but in the accompanying ulcerative process. The secretions from the growths, especially if confined under dressings, may have eroded and destroyed the surrounding skin, and it is tempting to interpret a recession of the associated ulcerative disease as an indication of a favorable effect on the new growth. It is unquestionably this aspect of rodent ulcers which plays so generously into the hands of the numerous nostrum venders for this disease.

"In brief, the demonstrable reduction in size of a tumor, of a kind not to be attributed to the natural processes of evolution of that tumor or of its associated lesions, is the one essential feature of effective therapeutic intervention."

In other words, so many substances, like various socalled synthetic chemical compounds, specific serums, vaccines of cancer cells, tissue autolysates, etc., may temporarily influence the associated symptoms of malignant tumors and, in exceptional cases, even bring about temporary or permanent regressions, that great care is required in accepting any of them as truly curative of the disease. It is not surprising that colloidal shock reactions, elicited by protein agents or the heavy metals, may produce inflammatory reactions about the tumors with improvement in pain or hemorrhage but, as stated by Weil, these alone are not to be accepted as criteria of cure.

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Arthritis and Amiodoxyl Benzoate

(A Review of Recent Literature)

By D. L. Tabern, Ph.D., *Lake Bluff, Ill.*

ARTHRITIS is the oldest disease entity of which we have historical record; arthritic disorders affected men in the stone age, and even the animals of prior times. The extent of its ravages at the present is hardly realized. For instance, in Berlin the disability resulting from arthritic and rheumatic disoders exceeds that from tuberculosis in the ratio of three to one (*J.A.M.A.* 91, 30), while the number of cases is eight times as great.

In England, particularly, the striking prevalence of rheumatic fever among children is commanding well-deserved attention. The importance of the problem lies, not so much in the immediate loss and suffering, but in the fact that serious cardiac disturbance is a common end result.

Just prior to the World War, there began in England a determined movement to initiate a careful study of arthritis. This work has recently been resumed on an international scale. An American Committee of 17 held its first meeting in Philadelphia on March 17, 1928; several recent conferences of European investigators will receive more detailed mention later in this paper.

Infectious Origin

While our knowledge of the etiology of arthritic processes is extremely imperfect, it now seems certain that the great majority of cases are of infectious origin. This fact places the solution of the problem of prevention and cure squarely upon the shoulders of chemotherapy and bacteriology. It is the purpose of this paper to summarize some of the more recent contributions which these sciences have made toward the treatment of arthritis.

Crowe, in his recent volume ("Treatment of Chronic Arthritis and Rheumatism") attempts to establish the staphylococcus, *Micrococcus deformans*, as the causative agent in rheumatoid arthritis, while osteoarthritis he attributes to the activities of a streptococcus. Normally both bacteria may be present in the host, giving rise to the socalled mixed types, wherein first one and then the other organism becomes predominant.

Most workers, however, attribute arthritic conditions much more exclusively to the activities of streptococci. Hadjopoulos (*Jour. Bone & Joint Surg.*, Apr., 1927) has reported some 40 cases where these organisms were isolated from the blood stream of arthritic patients and then injected into rabbits, where they produced typical joint changes.

Small (*Am. J. of Med. Sci.*, May, 1928) has recently announced the discovery and isolation of *Streptococcus cardioarthritidis* from the blood and exudates of a number of patients suffering from rheumatic fever. Following the observation that this microbe also caused typical lesions, upon inoculation, he has developed specific antisera and antitoxins, and has employed them in the treatment of a moderate number of patients. The reactions observed were unfortunately quite severe.

Birkhaug (*Proc. Soc. Exp. Biol. & Med.*, Mar., 1927) has also studied a somewhat similar streptococcus.

Granting, then, the bacterial origin of the disease, knowledge of the mode of entrance of the organisms and of their growth and transfer becomes necessary for their eradication. Sir Humphry Rolleston and others have placed the responsibility of the teeth and tonsils as foci of infection as high as 80 to 90 percent. Wilcox assigns 13 percent to intestinal and 5 percent to urethral causes. Lockwood and Skinner (*Radiology*, July, 1928), in studying 1500 patients, observed that 168 showed definite evidence of infectious arthritis. In 111 of these, gall-bladder disease was found, this frequently being the only demonstrable focus of infection.

Especially in atrophic arthritis, following the menopause, endocrine disturbances, no doubt, play an important part.

The mode of transfer of the organisms within the body and the mechanism of their action remain obscure. If we agree with Coombs (*Brit. M. J.*, May 19, 1928) that the infection is blood-borne, we are faced with the anomaly that normally but few bacteria can be found in the blood stream. Again, the joints—the active sufferers—are usually quite free from infection.

Rather, it seems, we must rely upon the conception of primary and subsidiary foci of infection from which toxins are liberated into the blood stream. Pemberton and his associates have demonstrated the ease with which such substances pass from the blood to the synovial fluid, while Fisher has shown that sterile synovial fluid from an early case of osteoarthritis, upon injection induced degenerative changes in the articular cartilage of a second animal.

Treatment

Less progress has been made in the effective treatment of arthritis. When we appreciate its many causative agents and the many forms which the condition may assume, it becomes obvious that we must seek to design a treatment for each particular type of the disease.

In frankly infectious arthritis, where foci of infection may be located or where their presence is apparent, the first step is the removal of these foci as completely as possible. The necessity for this is obvious, since a continued outpouring of bacteria or toxins may ultimately defeat the most effective measures at our disposal. Today, with our extensive list of diagnostic procedures, this does not mean merely the removal of suspected teeth and tonsils. Unfortunately, by the time most patients come to treatment, the organisms have spread to less accessible locations. Full use must therefore be made of cholecystography, liver and kidney function tests, gastrointestinal examination, and a study of the urinary tract, before a definite opinion can be formed.

It might seem that arthritis offers unusual possibilities for the use of vaccine treatment; yet, experience has seemingly failed to substantiate our hopes. Crowe, in his volume mentioned previously, describes in great detail the methods employed by him. Wilcox (*Brit. M. J.*, May 19, 1928), has very recently discussed this mode of medication before the Bath Conference on Rheumatic Diseases. Jeffry has also contributed an important paper to be found in *Northwest Medicine* for June, 1928.

Autogenous vaccines, prepared from as

many foci as possible, seem best, though on account of the difficulty of this procedure, stock vaccines are most commonly employed.

A second severe drawback is the selection of a suitable dosage. Too great a number of bacteria leads to severe and frequently harmful reactions; on the other hand, too small a number fails to induce improvement. Moreover, the dosage must be gradually increased over a long period of time, during which unavoidable variations in sensitivity may lead to sudden reactions difficult to interpret. Foreign protein injections have been used with some success, but do not seem to have met with widespread favor.

Until recently, chemotherapy made but few contributions to this problem. Iodine has been employed empirically in many types of combination (See *J. Chemotherapy*, Jan., 1927, p. 32) without marked success.

The use of salicylates in small doses, to relieve pain, and in massive doses, to control the infection, has been and still is of considerable importance. Without question, relief from pain is of prime importance, particularly in acute cases, but where the use of analgesics leads to a false impression of clinical progress, they may be responsible for much damage. It has been repeatedly emphasized that the salicylates must be pushed to the tolerance of the patient in order to secure the best results.

Recently, combinations of cinchophen (or neocinchophen) and an analgesic-like amidopyrene have found use, particularly in those cases complicated by disturbances of normal metabolism.

Action of Iodoxy Benzoic Acid

The first distinct contribution of chemotherapy to the treatment of arthritis is the synthetic medicinal, o-iodoxy benzoic acid, introduced by Young and Youmans and used, preferably in the form of its ammonium salt, Amiodoxyl Benzoate. During the three years that this drug has been available, it has been the subject of some twenty articles reporting approximately 600 cases. Of these, more than 70 percent have shown moderate to marked improvement, while a further 15 percent have been distinctly benefited. While much remains to be learned regarding its mode of action, the following facts have been rather thoroughly established.

1.—It has a definite bactericidal action in the blood stream, and perhaps in infected tissues and membranes as well.

2.—It has been shown experimentally that it stimulates leukocytosis and aids antibody formation.

Iodoxy benzoic acid possesses available or germicidally active oxygen, stabilized sufficiently to permit injection into the blood stream. In this drug, therefore, there exists a logical and effective means of combating an active blood stream infection, such as exists in acute rheumatic fever.

The stimulation of leukocytosis and antibody formation offers a further effective mode of strengthening body defenses, without the injection of foreign proteins or vaccines.

3.—Iodoxy benzoic acid and its salts strikingly increase the permeability of membranes.

4.—It increases lymph flow by 400 percent.

Since the joints receive their nourishment from the blood only through the agency of the lymph, and dispose of their wastes in the same way, any mechanism whereby lymph flow may be increased should promote the wellbeing of those members. In a similar manner, increased permeability of membranes makes for more rapid elimination of toxic products. In this connection it must be remembered, however, that this phenomenon will mean increased absorption of toxins from the intestines in cases of marked intestinal intoxication.

While distinctly not a salicylate, iodoxy benzoic acid does bear a certain chemical relationship to salicylic acid, possessing an (IO_3) group in place of the (OH) of the latter. While we might expect it to show some analgesic action, it is indeed surprising to find that this substance has a much stronger analgesic and antipyretic action than has salicylic acid. Thus, Smith has found it possible to accomplish with one gram of Amiodoxyl Benzoate what could not be done with massive doses of salicylates. We may say, then:

5.—Iodoxy benzoic acid has an intense and prompt analgesic effect.

6.—It decreases muscle spasm and reduces swelling.

As Jeffry has clearly pointed out, following the removal of foci of infection and the destruction of the active infection in the body, must come rehabilitation. Any member held inactive by muscle spasm or

even restrained in motion by intense pain will soon degenerate. In those deformative changes, where marked lipping and ankylosis has not made motion impossible, Amiodoxyl Benzoate, through its unique ability to reduce muscle spasm, is of marked value. In fact, if it were to do nothing more than enable the patient to resume careful active motion, its use would seem justified.

It has been found most advantageous to administer Amiodoxyl Benzoate intravenously, by the gravity method. The reactions, while sharp, have not led to permanent harm, and are certainly no more serious than those experienced in the administration of vaccines.

Whatever method is employed for stopping the infectious process, it must not obscure the necessity for the thorough and intelligent use of suitable physical therapeutic measures. Rather than being of less value today, preliminary application of the products of chemotherapy has made them more valuable. In this group will, of course, be found rest, together with regulated exercise, diathermy, massage, hydrotherapy, ultraviolet rays, etc.

Certainly recent developments in our knowledge of the causes of arthritis, and the elaboration of improved modes of treatment, have made the present outlook for the arthritic patient much more promising than ever before.

Chemotherapy of Metals, with Special Reference to Tellurium

By M. SEVERAC, M.D., *Philadelphia, Pa.*
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SINCE the discovery by Sazerac and Levaditi of the valuable curative properties of bismuth in experimental rabbit syphilis, that element has become an important aid in the treatment of syphilitic patients. It is now used very widely by syphilologists and excellent results are obtained, clinically and serologically. The use of the element bismuth is now at least as widespread and probably even more extensive than that of mercury in the treatment of syphilis. In view of the extraordinary success which resulted from the application of bismuth, the attention of research workers was attracted to other metals for utilization, not only in the treatment of syphilis, but also of other infectious diseases.

VANADIUM

Vanadium, which belongs to the same group of elements as arsenic and bismuth, has been studied by Fournier, Levaditi and Schwartz, in experimental animals and also in clinics, and found to be of value[1]. In 1924, Neuendorf[2] was reported to have obtained good clinical results in secondary syphilis by means of vanadium pentoxide, although the employment of this product was followed by injurious by-effects. Kroesl[3] claims that sodium orthovanadate, called Northovan, is a very effective remedy in syphilis. However, he did not employ this compound alone, but in combination with Stovarsol (acetarsone). Goldschlag[4] found that vanadium favorably influences syphilitic gummas.

Our own investigations in experimental rabbit syphilis indicate that vanadium possesses distinct curative effects and enjoys prospects of being employed as a successful antisyphilitic remedy. It is necessary, however, to produce new derivatives of vanadium with diminished toxicity and also with increased therapeutic efficiency.

Cadmium, in the form of an oil suspension of cadmium subsalicylate, was suggested for the therapy of syphilis by Grouven[5]. While good results were reported by some clinicians, Levaditi, Nicolau and Navarro-Martin[6] reported unfavorably on this element.

Many other elements, including antimony, silver, gold and selenium were investigated. Indeed, Levaditi[7] made a study of 21 elements. Most of them thus far have not proved to be particularly valuable.

TELLURIUM

A very interesting study of tellurium was carried out by Levaditi and his co-

workers. This element belongs to the sixth group of elements which, to date, are of no particular value in the treatment of syphilis; but it also belongs to the 5 – orbit series of elements, comprising such valuable metals as silver and antimony. The latter were found to be valuable as spirocheticides and also in the treatment of other infectious diseases, particularly those of protozoan origin. Therefore, tellurium, on the basis of the relationship of chemical elements, appears promising.

The researches of Levaditi point strongly to the possibility of employing tellurium as an antisyphilitic remedy. He utilized the element itself, suspended in a 5 percent glucose solution. It was found that tellurium can cure experimental rabbit syphilis and that it is of sufficiently low toxicity to permit intramuscular injection.

Fournier, Levaditi and Guenot[8], encouraged by the preliminary experimental results, applied preparations of tellurium in 40 cases of human syphilis. No pathologic phenomena were observed during the treatment, except a blue pigmentation of the integument and a garlicky odor emanating from the body of the patient. Six weeks after the last injection, the color as well as the odor were still present, though faintly. Occasionally, discoloration of the hair was observed when patients were treated with tellurium.

So far as the effect upon syphilis is concerned, the following is interesting: In the first case (one of efflorescent secondary syphilis), 3 injections of 1.5 cc. (0.3 gm.), 2 cc. (0.4 Gm.) and 2.5 cc. (0.5 Gm.) of a 20-percent solution of elemental tellurium in glucose were given within one week. The spirochetes disappeared from the lesions after the second injection, and in 20 days the syphilides, which had covered the entire body, were completely healed. The blood Wassermann reaction only became normal in 7 weeks, but no drugs were used in the interim. Smaller doses did not produce interesting clinical results.

The recent work of Levaditi[9] is also interesting. In order to study the preventive effect of tellurium, rabbits were given intramuscular injections of metallic tellurium or of tellurium trioxide in doses containing 0.025 to 0.1 Gm. of the element. Eight to 29 days afterwards they were subjected to inoculation with syphilis. If unsuccessful, the latter was repeated 80 to 108 days later. It was found that, if injected in sufficient amount, tellurium exerts a protective action lasting for at least 107 to 116 days. Chemical analysis of the tissues indicated that the animals which were protected longest were those whose organs, particularly the kidneys, contained the largest amount of tellurium; in those refractory to the second inoculation (116 days), the quantity of tellurium in the kidneys amounted to 1 milligram or more per gram of dry matter; in those which resisted only the first inoculation, the kidneys contained from 30 to 92 micrograms of tellurium per gram.

Encouraged by the laboratory and clinical reports on tellurium, we also performed a series of experiments with this element at the Dermatological Research Laboratories. We employed a suspension of the element in 5 percent glucose solution, as well as telluric acid and two derivatives of the same, viz.; tellurium urate and a combination of telluric acid and methenamin. All of these products, prepared by our own chemists, were studied for toxicity by the intramuscular and intravenous routes, while their therapeutic efficiency was determined in rabbits infected with *Spirochaetae pallida*.

In testing the toxicity of drugs by the intravenous route, healthy, non-pregnant white rats, weighing between 100 to 150 Gm., were given doses proportionate to their body weights. The injections were made after about 18 hours' fasting so as to render the dosage more accurate. The saphenous vein was employed, and the injection made by the gravity method with the aid of a special apparatus which permits of very accurate measuring of the volume of solution and also regulation of the rate of flow.

When the intramuscular route was employed, all of the above conditions were observed except that the injection was made with an ordinary syringe.

In testing the therapeutic efficiency of antisyphilitic drugs, rabbits previously (4 to 6 weeks) infected intratesticularly with *Spirochaetae pallida* were treated with a definite quantity of the drug, either intravenously or intramuscularly. The animals were kept under observation until the spirochetes disappeared from the testicles and complete cicatrization of the lesions occured.

A sensitive method of ascertaining whether or not the drug had cured the infected rabbit is to excise the popliteal nodes of the latter, convert them into an emulsion with sterile isotonic saline solution and inject into normal rabbits intratesti-

cularly. If the latter do not subsequently develop syphilitic lesions it is positive proof that the original rabbit was cured.

Elemental Tellurium (suspended in a 5 percent glucose solution).

The maximum tolerated dose of elemental tellurium, by the intramuscular route, was 0.09 Gm. per kilo of body weight, for white rats. Rabbits tolerated the same product intramuscularly in an even slightly higher dose (0.1 Gm. per kilo). Elemental tellurium, 0.05 Gm. was sufficient to produce a strong antisyphilitic effect. In one of our animals this dose caused a disappearance of the spirochetes from the lesions in 48 hours, and complete cicatrization of the syphiloma occurred in 25 days. The intramuscular injection of metallic tellurium gave rise to severe local pain and induration. In one of the animals it caused atrophy of the muscle. This induced us to experiment with tellurium compounds which are soluble in water.

Telluric Acid (H_2TeO_4, dissolved in water and neutralized with sodium hydroxide until faintly alkaline).

According to Levaditi and Nicolau, doses as small as 0.005 and 0.004 Gm. of telluric acid are very toxic for the rabbit when injected intramuscularly or subcutaneously. According to these authors the above doses produce hemolysis of the blood, causing profuse hemorrhage and hematuria. In rats, we found the maximum tolerated dose of telluric acid intravenously to be 0.05 Gm. per kilo of body weight, while rabbits tolerated 0.008 Gm. of telluric acid intravenously. Telluric acid, in dosage approaching the maximum dose tolerated intravenously by rabbits, caused a disappearance of the spirochetes from the lesions of syphilitic rabbits in 72 hours. In some cases spirochetes disappeared from the lesions in 2 days, while the testicles became normal in 2 to 3 weeks. In this respect tellurium yields almost as good results as bismuth intravenously.

The other two preparations, tellurium urate and the methenamin combination with telluric acid, also proved of distinct spirocheticidal value. The methenamin preparation of tellurium, intravenously in rabbits, induced death in a dosage of 0.01 Gm. (the maximum tolerated dose was apparently less than this amount). In rabbits, the maximum tolerated dose, intramuscularly, was close to 0.015 Gm. The intramuscular injection of this product caused pain and induration. Tellurium urate was tolerated by rabbits, intramuscularly, in a dose of 0.02 Gm., and this compound also caused pain and induration. It is interesting to note that tellurium urate, administered intramuscularly to a syphilitic rabbit in a dose of 0.02 Gm., produced a disappearance of spirochetes from the lesions in 4 days, and the testicles became normal in 18 days.

In animals which die of tellurium poisoning the following changes are particularly noticeable: A strong, garlicky odor emanates from the viscera, and most of the larger internal organs are black in color, indicating a deposition of the metal. As revealed by macroscopic examination, the organs affected are primarily the kidneys, then the intestines, liver, spleen and lungs. The viscera become colored even if a nontoxic dose of tellurium is administered. Thus, one of our rabbits, which received 0.1 Gm. of elemental tellurium, was killed 133 days later; upon autopsy we found that the kidneys were very dark blue on the outer surface and cortex, a small part of the intestine was blue and the brain slightly gray, while a very strong odor of garlic was noticeable.

Elemental tellurium, injected intramuscularly, is apparently eliminated very slowly. However, the retention of tellurium in the body does not interfere with the well-being of the animal; the rabbit discussed above gained 320 Gm. (17%) in weight in 110 days.

The blackening of the viscera, particularly of the kidneys, after tellurium poisoning was also observed by Levaditi and his co-workers. By chemical analysis of the tissues of animals treated with tellurium compounds, they found that generally the kidneys contain a larger amount of the element than any other internal organ, except the spleen, which may sometimes be even richer in the metal than the kidneys. They also noticed that "black kidneys" did not preclude substantial gains in weight by the affected animals.

Conclusions

Heavy metals have opened up a new field in the chemotherapy of syphilis and in the treatment of infectious diseases generally.

Experimentally, tellurium compounds exert a strong antisyphilitic action, but large doses of this element must be given in order to obtain results.

Intravenously, tellurium is no more toxic than bismuth; however, both elements are too toxic to be used in actual therapy by this route.

The great advantage of bismuth compounds is that their toxicity is very low when given intramuscularly. The animal body apparently effects a change in the bismuth compounds, rendering them considerably less toxic. This does not happen with tellurium. The toxicity of the latter compounds by the intramuscular route is not much lower than by the intravenous route. Furthermore, tellurium administered intramuscularly is painful and causes induration. The same element has a specific effect upon the kidneys, the kidney substance assuming a distinct black appearance. Even doses of this metal which are not fatal to the animal cause coloration of the kidneys.

Tellurium should be classed in the group of drugs possessing valuable spirocheticidal effects in vivo. The preliminary experimental work with this metal suggests possibilities for the production of new compounds which may be of service in the treatment of syphilis.

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Chaulmoogra Oil and Synthetics in Leprosy

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NOT two days journey from San Francisco, as Lindbergh flies, is Manila, historic city of the Philippine Islands. Less than two hours more by air, to the south of Manila, lying on the windy edge of the China Sea, on the island Culion, is the largest leper colony in the world. Here, under the American flag, 6,000 lepers are segregated and undergoing treatment. Over 6,000 more lepers are going through their living death in other parts of the Philippine Islands at the present time. Thus we see that leprosy represents a problem of today, to the United States, just as it has been a problem to mankind since the earliest times in history.

Leprosy is prevalent throughout Asia, from the Mediterranean to Japan, and in nearly all parts of Africa and India. The Chinese introduced it into Australia and the Hawaiian Islands, where it has developed extensively. Within our own boundaries there are a few lepers in Louisiana and California and among the Norwegians of the Northwest. It is estimated that there exist today over three million lepers in the entire world.

The scientific development of the treatment of leprosy has been carried out almost exclusively in Hawaii, the Philippines, and Calcutta. A colony of lepers exists at Kalihi, in Honolulu, where a few hundred cases are being treated continuously, and a scientific study is being made, in cooperation with the University of Hawaii.

The large, well-known leper colony at Culion is established in such a way that many of the leper patients can take an active part in the administration, more than half of those employed in administrative positions being lepers. In addition there is a large staff of non-leper physicians, nurses and aids.

Leprosy is one of the most serious problems facing the Philippine government and, incidentally, the United States. This may

be seen when it is considered that $600,000 a year—2 percent of the entire revenue of the Islands, and one-third of the Health Service appropriation—is given over to the treatment of leprosy. At present, in the United States, a concentrated effort is being made to obtain gifts to the amount of $2,000,000 for a fund to be known as the Leonard Wood Memorial for the Eradication of Leprosy. It has for its purpose the eradication of leprosy throughout the world by developing the resources and equipment of the leper colony at Culion, with the end of perfecting the most effective procedure in treating leprosy.

The disease is due to the *Bacillus leprae*, which was isolated, in 1874, by Hansen. The mode of transmission of the disease is not well understood. It is certainly contagious, as it is always found in people brought socially together. It is not hereditary, if recent work reported from Culion is correct. New-born babes, if taken immediately away from leper-mothers, do not contract leprosy.

The disease may extend over a period of 20 years, if the patient is cared for, and sometimes recoveries, without any special treatment, are reportd.

The treatment of leprosy, until very recently, has been empiric, and is largely so even now. In general, the patients are given a full diet, care is taken that they receive digestible foods, hot baths are administered and particular care is taken against complicating diseases, such as malaria, pleurisy and pneumonia. The patients are almost always given a tonic, and in addition receive a chaulmoogra oil treatment.

It has now been definitely established than non-medical treatments are utterly inadequate in the absence of medicinal treatment. The chaulmoogra oil treatment is the only one known which has been found to be of distinct aid to patients with this disease. A considerable portion of those patients who are discovered within the first six months after infection, can be cured by the general treatment just mentioned. In fact, over 1,000 of the milder cases have been cured during the past five years at the leper colony at Culion. The older cases are relieved, but the percentage of cures is small.

Chaulmoogra Oil

The use of chaulmoogra oil and other oils of similar character has developed from the observations, noted during the past several centuries, that natives in the Far East, afflicted with leprosy, knew that they received relief by rubbing the wounds with the oil and by its oral administration.

The date of the discovery of this oil and its efficacious properties is unknown. It is like so many of our most important medicinal substances at the present time: They have come down to us from uncivilized peoples and, in spite of the advances of science, nothing has been found which can surpass them. Quinine, morphine, and strychnine may be mentioned particularly in this connection.

The chaulmoogra oil used in the treatment of leprosy has, until very recently, almost always been secured from the fruit of the *Taraktogenus kurzii*, which resembles the grapefruit in appearance and, when cut open, is found to contain irregular-shaped seeds. These seeds are pressed and the crude oil, which is a thick, semi-solid, yellowish-brown mass at room temperature, is obtained. Other oils of importance are those of the *Hydnocarpus wightiana* and *Hydnocarpus anthelmintica*. With the increased interest, other sources have been sought and many species of plants have been discovered during the past fifteen years which contain oil of a similar character and usefulness.

In the olden times the first treatment was percutaneous, along with internal, administration. The oil, however, causes rather violent intestinal disturbances, with nausea and vomiting. It was a superstition among the natives that if a patient could take the oil without becoming sick, he would get well. This is not true, though many of the patients were materially improved.

It was not until 1899 that any attempt was made to study chaulmoogra oil from a medical or chemical standpoint. At that time an attempt was made to inject this oil subcutaneously. A marked improvement in the patient was generally noticed, but the injection proved to be very painful. This was generally assigned to the fact that the oil, being so thick, was slowly absorbed.

As a result of this early observation, many physicians offered preparations which were less viscous. Thus, one of the first suggestions was the admixture of chaulmoogra oil with olive oil. This was followed by a number of others, of which

that proposed by Heiser gave the most success. His formula was composed of camphorated oil, chaulmoogra oil and resorcinol. From the years 1899 to 1918 this was the favored remedy. Just recently, however, it has been definitely established that, if refined chaulmoogra oil or, especially, the oil heated with one-half percent iodine is used, this is superior to any of the admixtures previously prepared, and a minimum of irritation occurs.

The Sodium Soaps and Esters

In 1918 Dr. Rogers, a prominent British surgeon in India, converted chaulmoogra oil, by means of caustic soda, into the corresponding soap, just as palm or olive oils are converted into ordinary soap. The soaps or sodium salts were dissolved in water and the solution injected—first subcutaneously, then intramuscularly and finally intravenously. This treatment proved more satisfactory than any that had hitherto been given, and is still used to a certain extent in India and China, in the leper colonies.

About the same time Dean, president of Hawaii University until very recently, but at that time a member of the chemistry department, converted chaulmoogra oil into the *ethyl esters* of the mixed acids of the oil. The esters thus obtained are very much less viscous than the oil, and were administered intramuscularly with much success. This treatment is used extensively in the Philippines and Hawaii at the present time.

Although the effectiveness of the treatment of lepers has probably increased an hundredfold during the past ten years, the real advance in their treatment has just begun. During the past a careful study of the treatment has been rendered difficult because of the great differences and nonreproducibility of the natural oils used. The hope of the leper is much more likely to lie in the discovery of synthetic products which are more efficacious than the natural, and which may be carefully standardized and altered to meet the definite needs of the leper patient.

Synthetic Substances

The organic chemist has studied that portion of chaulmoogra oil which has the curative effect—the chaulmoogric acid molecule—in such great detail that its internal structure is now known. The acid consists of a five-carbon, unsaturated ring, with a side-chain of thirteen carbon atoms having the carboxyl group at the end. *This acid has been synthesized in the laboratory,* but its cost is too great to make the synthetic product of practical value. The organic chemist has further interested himself in seeking a compound more satisfactory than chaulmoogra oil in bactericidal action toward *B. leprae,* and yet a compound not so expensive as to exclude its manufacture as a commercial possibility.

In order to determine the portion of the chaulmoogric acid molecule which is responsible for the bactericidal action toward *B. leprae,* hundreds of compounds similar in structure to chaulmoogric acid have been synthesized at the University of Illinois and tested in vitro against the leprosy bacillus. Tests have been made using all the known strains of the leprosy bacillus and also using bacilli of a similar nature, such as the tubercle and smegma bacilli. These tests have led to the synthesis of compounds having a distinct bactericidal action toward *B. leprae,* yet possessing a structure bearing but slight resemblance to chaulmoogric acid. The ring has been altered to contain from three to six carbon atoms, or has been left out entirely; the carbon chain has been shortened or lengthened; and the position of the acid or carboxyl group has been moved along the chain, and the effect of each of these changes has been carefully determined by bacteriologic tests. The effect of the presence of halogens, olefinic linkages and hydroxyl or amino groups is being studied.

One of the most interesting results of the work is the apparent prime importance of solubility and molecular weight. The bactericidal action and, incidentally, the solubility, appear to reach a maximum when a molecular weight corresponding to a total of about sixteen to eighteen carbon atoms is reached, in the acid molecule. The type, or even the presence, of a ring in the molecule appears to be of secondary importance. The position of the carboxyl group appears to be of significance. It, apparently, modifies the physical properties of the molecule and thus alters the bactericidal action. In fact, the bactericidal action of this type of chemical compound may depend almost entirely upon physical properties, such as solubility and surface tension of the molecule. Tests are under way at the present time to

determine the correctness of this hypothesis. It is hoped that it will soon be possible to draw definite conclusions as to the structure of a compound which may be the most efficacious in the treatment of leprosy.

The toxicity of these compounds is of a relatively low order. Dr. C. B. Lara, of the Culion Leper Colony, is kindly making the clinical tests. Unfortunately, the treatment of the leper patients is a very slow procedure, extending over a period of at least two years before a reliable statement can be made as to the results.

The task of synthesizing a compound of sufficiently high bactericidal action toward *B. leprae*, with sufficiently effective penetration into the lesion and sufficiently low toxicity to the patient as to constitute a marked advance beyond the present known remedies, appears to be well on the way, although the amount of work yet remaining is almost inestimable.

The organic chemist has laid a good foundation upon which future work may be based, and there is no question that, sooner or later, scientific study and research will succeed in finding a remedy which, even if it does not entirely eradicate the disease, will at least relegate most of its horrors to the past.

Gonorrhea and Its Chemotherapeutic Treatment

By G. M. Russell, M.D., *Billings, Montana*

THE article of Bennardi, and that of Ferguson, on artificial leukocytosis in the treatment of gonorrhea, in the June, 1927, number of Clinical Medicine and Surgery, will cause any man who has had many such cases to handle to think of his own experience with that disease.

The basic pathologic condition, we have been told, by men who know what it is, if any one does, is the deep infiltration of the gonococcus into the mucous and submucous tissues. Upon the virulence of the strain with which the subject is infected and his resistance, depend the depth to which the gonococcus will descend.

Truly, each case is different, and that difference depends upon the virulence of the infection and the resistance of the patient and so, the depth of infiltration; upon the area infected; upon the region infected; upon extensions to prostate, seminal vesicles and epididymis and their surrounding tissues. It is not unreasonable to assume that infiltration into the deeper tissues exists wherever there has been infection.

When one becomes so efficient in diagnosis that he can determine, by any kind of an examination, all the points enumerated, he can, perhaps, outline the identical treatment proper for each particular case; but until he can do so he is groping in the dark, just the same as we always have done —floundering around, grasping for something that will terminate the trouble.

There may be men who are so highly endowed as to be able to minutely determine all these points, and so pounce upon the identical remedy and methods of treatment in every case. But even then, there are liable to be cases in which the infiltration is so deep that their remedies will not reach the invading bacteria. There will be encysted glands and inflammations of lacunae that will elude the average man, and infiltration into tissues which do not come within the spheres of action of dilatations, urethroscopic applications or deep instillations.

Until one has become such a paragon that he can tell just how far an infection has extended, just what tissues are involved, and how much and how deep into those tissues the gonococcus has delved, he need not congratulate himself on being able to cure any cases. Gonococci, beyond the reach of drugs, continue to exist and propagate. If remedies cannot come in contact with the gonococci there can be no hope of destroying them.

Inefficiency of Local Treatment

A study of a dozen or more authors reveals the fact that no two of them agree on methods of treatment; and when the galaxy of remedies purporting to be effec-

tive is considered, it is easily determined that no one remedy or combination of remedies has been in any measure satisfactory in the treatment of this disease.

I have treated cases of posterior gonorrhea by all the methods usually advised, including diathermy, and those recommended by Bennardi, until I have become tired of seeing them come to my office, and eventually they have gone elsewhere, to have the same series of treatments repeated.

In the fall of 1919 Hugh Young and his co-workers originated Mercurochrome[1]. I had marvelous results with it in a short series of cases. One patient who had had the disease for three years and had been treated in the Army and by several good civilian physicians, I rendered germ-free in two weeks. But a few months later I was not getting those results, and have not done so since. A representative of Hynson, Wescott & Dunning told me that others had had a similar experience. How is it to be explained? Hugh Young states[2] that it does penetrate into the mucosa, even as much as 2 mm., and has powerful germicidal powers; that, in view of these facts, the results in acute gonorrhea have been disappointing, indicates that the infection is too deep seated, in many cases, even for this penetrating agent.

Herrold and Culver[3] claim for their solution of acriflavine in a 10-percent of gelatin, an average time until cure of 3.2 weeks. I have used this in several cases, but with no encouraging results.

I used mercurochrome intravenously, according to the Whitman method[4], in six cases. I could never find any gonococci in any of them, although, a year afterward, one had a recurrent epididymitis, and insisted upon another course of the same treatment, since which time he has had no trouble. The reaction to mercurochrome used in this way was so severe that I discontinued it. I have since read of fatalities from it.

Redewill, Potter and Garrison[5] published a method for the intravenous use of mercurochrome in a 50-percent solution of glucose. While there is no reaction to speak of from this combination, it is a disgustingly sticky mixture to handle, so much so that the plunger adheres to the barrel of the syringe.

Brandan, of Argentina, uses a daily intravenous injection of 5 cc. of a 2-percent solution of tripaflavine, which is equivalent to acriflavine. He states that gonorrheal therapy has been reinforced with a powerful remedy, superior to any known up to the present time for ease of application, comfort of the patient and indisputable, specific germicidal action on the gonococcus, which it destroys and removes, little by little, from the innumerable glands of the urethra. I have used this only as an adjunct to the treatment I am now employing.

Efficient Parenteral Treatment

J. E. R. McDonagh[6] has had considerable experience in the treatment of gonorrhea with the symmetrical urea of meta-benzoyl-meta-amino-benzoyl-amino-naphthol-3-6-sodium sulphonate, or "sum 36" for short, giving two intramuscular injections of 2 mgm, at five-day intervals, the two injections to be followed by a course of vaccines. In complications he uses the symmetrical urea of para-benzoyl-para-amino-benzoyl-amino-naphthol-3-6-sodium sulphonate or "sup 36"; two injections of 10 mgm, at three-day intervals, to be followed by one or more courses of vaccines; but in cases of epididymitis and salpingitis the vaccines should be preceded by an intramuscular injection of .25 Gm. contramine. He uses from 1,250 million to 5,000 million of gonococcus vaccine, at two- to seven-day intervals.

I have now been using these products for a year and a half, and I have not failed to render a single case germ-free during that time. I have not, in that time, had a single complication, which is more than I can say for any method I have used before. The only change I have made in McDonagh's method is that, to the gonococcus vaccine, I have added 5 cc. of Lactigen (boiled milk) or 1 Gm. of peptone in 10 cc. of water, given intramuscularly. I give twelve of these injections, two days apart.

Testing for Cure

After completing this course, the patient is tested. He is instructed to come to the office when he has not passed urine for at least five or six hours, preferably before he passes urine in the morning. The prostate is then massaged and the urethral canal stripped, causing the prostatic fluid to be discharged from the meatus. A culture is made from this, the culture medium

used being litmus-dextrose-ascitic-agar. Gonococci will grow only on ascitic fluid or blood plasma.

There are two Gram-negative diplococci that cannot be differentiated from the gonococcus under the microscope; they are the meningococcus and the diplococcus catarrhalis. The meningococcus may be disregarded, as it is not very likely to be found. The gonococcus forms acid when grown in the presence of dextrose, so that, with the addition of dextrose and blue litmus, if the inoculated culture turns red, and diplococci are found in the smear from it, they are evidently gonococci. As an additional safe-guard, a culture is also made on plain nutrient agar. If Gram-negative diplococci are on both cultures, and the litmus-dextrose-ascitic-agar does not show acid, gonococci are not there and the growth is diplococcus catarrhalis; if acid forms, there is a gonococcus growth, but the diplococcus catarrhalis is also present. If the growth is only on the ascitic medium, with formation of acid, it can be none other than gonococci. I have these tubes made up ready for use. The nutrient agar tubes are staple articles.

Gradwohl[7] has brought out a new culture medium. It is more troublesome to use, and it is doubful whether the results are any better.

I came to the conclusion, years ago, that the eventual solution of the problem would be some form of medication that would attack the gonococci through the blood stream, and I believe such a form has been found. From the experience I have had with the treatment I am now using, I would not return to the indefinite, hit-or-miss, gambling methods of urethral treatments which are generally being used. I believe the chances of success with the urethral route methods are just about equal to those of winning at roulette or craps, and based upon an equal amount of science.

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Manganese Butyrate in Furunculosis

By E. L. Touhy, B.A., M.D., F.A.C.P., *Duluth, Minn.*

The Duluth Clinic

CHEMOTHERAPY had its origin more or less empirically. The use of cinchona and its derivatives in malaria is probably one of the earliest examples. We may state briefly that it proved to be so useful that nothing up to date has taken its place. The arsenic compounds may be said also to have developed empirically, but the empiricism was of the laboratory rather than of active, daily medical practice.

It is well known that various metallic compounds have been given the widest experimental use in various types of infection. "Boils", from the time of Job, have been more or less universal, and have long challenged the attention of all—physicians and laity. Among the latter, all sorts of treatments and hopeful remedies have been suggested, many of them more disgusting than effective. With the certainty established in the minds of many that these external abscesses were only the effort of Nature to cast off "inward corruption," it was not unnatural that a plan to "purify the blood," in some manner or other, should have been the incentive and the therapeutic test.

It is interesting that a more thorough acquaintance with the staphylococcus establishes the layman's early conviction that there was within the body and in the blood a skin-erupting invader. One need not refer more than casually to the various spring tonics, including bromide and iodide salts, well qualified to produce skin eruptions and thus to convince even the most doubting subject, that he was full of "inward corruption."

Within recent years, however, we have come to know that there is a very definite connection between a "crop of boils" and

certain dangerous, hidden, hematogenous implantations in the inner organs, that show the menace to life of a staphylococcemia. The two most devastating are perinephritic abscess and osteomyelitis. To these may be added other, much more rare, disasters, such as endocarditis, and possibly arthritis The connection with perinephritic abscesses is, at times, so puzzling and so easily overlooked (if we do not question the patient very closely as to his having had furuncles), that the connection is entirely lost and misunderstood.

Therefore, even if some feel that furuncles are largely a nuisance and do not consider the individual's comfort of any remarkable moment, we may view these complications with enough concern to make us interested in any form of treatment that gives us empirical results, even though we may be in a good deal of doubt as to how it works, immunologically.

Accordingly, I submit for your consideration and trial, that for about four years, in the Duluth Clinic, we have followed the advice of a confrere who stated that two hypodermic doses of a 1-percent solution of manganese butyrate*, given at four- or five-day intervals, sufficed to cure most cases of furunculosis. This has proven to be true. Apparently about 70 to 80 percent of the cases respond favorably, particularly if the blood sugars are not running too high and the individual has no other obvious constitutional handicaps. We have found it quite as effective in the deep carbuncles as in the superficial furuncles. It seems far more efficient than the ordinary treatment with low carbohydrate diet and yeast. The patient's comfort is immediately promoted, and for the most part incisions and drainage are not needed. Those accumulations already close to the surface rupture spontaneously, and soon dry up. A short reference to an actual case recently treated will illustrate the method:

Case.—A. K., widower, aged 56 years, came March 10, 1928, complaining of severe pain in the epigastrium, and there had been some question as to the possibility of gall-stones. His history was rather indeterminative, but he made no mention of his furunculosis.

On stripping him for examination, we found an ugly flaxseed poultice over the axillary region on the left, and several large, distressing and discharging furuncles in the skin area below and outside the nipple, around to the axillary line. It then became perfectly obvious that his epigastric pain might well be referred from his furunculosis.

He was given the first dose of 1 cc. of the 1-percent manganese butyrate solution, his poultice was taken off, and a simple dry dressing applied. Four days later he reported that he had a good sleep the night after his first injection, and that the following day he could note a definite difference in the size of the furuncles and the angry appearance of the general skin area.

A second dose of 1.5 cc. was given, and he was told to return in eight days if any fresh furuncles appeared. He returned in eight days with all the original furuncles entirely cleared up and the skin area healing. There were, however, some smaller pimples in adjacent zones of softening, that most certainly would have been good, definite boils, under any method of poulticing and softening. He has since remained entirely well.

Up to date we have seen no benefit in other staphylococcic conditions, where, however, the question of etiology may always be taken into consideration and mixed infections are a great probability.

*We have used Mallinkrodt's 1-percent in saline solutions, with 0.5 percent cresol.

Power and Peace

It is entirely possible to have power and peace together. In fact, peace is the measure of power.

We must do our work in the RIGHT WAY *and* JUST ENOUGH—*not more than we can do* PEACEFULLY.

Assistance is always at hand. Let us PUT UP A SAIL *and not* ROW *too hard.*

Let us have more WILL *and less* WISH. *Wishing is always an acknowledgement of incapacity.*

*Any road is short that leads to our goal. It may be ten miles long—*OR SHORT, *according to our inner attitude.—Ernest Wood.*

THE SEMINAR

[NOTE: Our readers are cordially invited to submit fully worked up problems to the *Seminar* and to take part in the discussion of any or all problems submitted.

Discussions should reach this office *not later* than the 1st of the month following the appearance of the problem.

Address all communications intended for this department to *The Seminar*, care CLINICAL MEDICINE AND SURGERY, North Chicago, Ill.]

PROBLEM NO. 9 (SURGICAL)

PRESENTED BY DR. MAX THOREK, CHICAGO

(SEE CLIN. MED. AND SURG., AUG., 1928, P. 595)

Recapitulation: A male pateint, aged 30 years, has suffered for some time with attacks of epigastric pain, belching and some vomiting.

On admission he complained of severe abdominal pain for 3 days, at first diffuse but now localized over McBurney's point. Complete obstipation for 24 hours. Some vomiting. The abdomen was distended; tenderness over McBurney's point; rectus muscles rigid, more so on the right. Temperature 100°F.; pulse 110; respirations 24; blood pressure 146/100; leukocytes 21,000, with 84 percent polymorphonuclears.

Requirements: Differential diagnosis and therapeutic suggestions.

DISCUSSION BY DR. J. R. STURRE, MINNEAPOLIS, MINN.

The differential diagnosis of this case is:

1.—Perforated duodenal ulcer.
2.—Ruptured gall-bladder.
3.—Acute pancreatitis.
4.—Intestinal obstruction.
  A.—Volvulus.
  B.—Intussusception.
5.—Perforated gangrenous appendicitis.
6.—Diverticulitis.

By elimination:

The patient has rigidity of the lower recti, with pain localized at McBurney's point, and knees flexed on the abdomen. This almost eliminates an upper abdominal lesion.

1.—*Perforated duodenal* ulcer has a different history: sudden severe pain, shock and tachycardia, followed in a few hours by distention of the abdomen, giving tympany, generalized rigidity and pain, due to peritonitis, unless it localizes in the upper abdominal cavity.

2.—*Ruptured gall-bladder*: The history is not in accordance with this diagnosis. No previous gall-bladder symptoms; no pain or rigidity in gall-bladder region.

3.—*Acute pancreatitis*: The history bears this out, for the first 3 days; after that, localization of pain, etc., do not suggest this lesion as a probability.

4.—*Intestinal obstruction*: (A) *Volvulus* cannot be completely discarded, as I have a case in my records which, after careful study, I operated upon for acute perforated appendicitis. (B) *Intussusception*: The history is not in accordance. Both these lesions can be eliminated by the free catharsis, except during the last 24 hours, but remain as possibilities.

5.—*Perforated gangrenous appendicitis*: The rigidity of the recti, most marked on the right, and localization of pain at McBurney's point, especially in a male, along with a temperature of 100°F. and a pulse of 110, are probably due to appendicitis.

The chest conditions are eliminated by examination, and the respiratory rate of 24 can be accounted for by the type of breathing due to rigidity, tenderness and distention.

The distention, dry tongue, flexed thighs and legs mean marked peritoneal reaction.

6.—*Diverticulitis* must remain as a possibility. It might be ruled out or proven by x-ray examination with a barium enema.

Laboratory findings (I consider these last, as they are only an aid to the clinical findings):

The urine findings are possibly due to severe infection anywhere in the body; also the blood pressure bears out a probably chronic kidney lesion. To me, the indican has no meaning in differential diagnosis. The leukocyte count of 21,000, with 84 percent polymorphonuclear neutrophiles, means infection and *pus*.

My diagnosis is *acute gangrenous appendicitis, perforated.*

Treatment: Immediate operation, with drainage, followed by retention enemas—one given before the patient is awake—of 5-percent glucose (dextrose) with 5-percent sodium bicarbonate in isotonic saline solution.

If much absorbtion of toxic material is present and the patient is septic, I would give, intravenously, hypertonic sodium chloride solution, before operation.

I would use morphine, in ¼-grain (16 mgm.) doses, as needed, in a male 30 years old.

I do not withhold all fluids by mouth; rather I give the patient warm water, plain or alkalinized, by sips.

I would use Fowler's position, exaggerated with pillows under the knees.

If good drainage occurred after 48 hours, I would remove the tubes, at least partly, and turn the patient on his abdomen for 10 minutes daily.

Discussion By Dr. J. R. Smith, Warsaw, Mo.

From the beginning to the final history, the symptoms all point to *appendicitis.* It is, without a doubt, a surgical case, under the circumstances.

In country practice, miles from a hospital and with poor roads and inadequate transportation facilities, it is sometimes necessary to treat cases medically, which should properly be referred to a surgeon for operation; and the results are often satisfactory. I, myself, went through an attack of appendicitis and recovered, under medical treatment; but surgery would have promptly put an end to symptoms which required six years of careful diet and therapy to overcome.

The therapeutic stage of appendicitis (like that of cancer) is at the very earliest sign of distress—two or three years prior to the critical, fully developed attack. I give mineral oil in 2- to 6-ounce doses; compound sulphocarbolates, 5 to 50 grains, in hot water; and laxative tablets containing bile salts three times a day. The diet should be very carefully regulated.

Solution by Dr. Max Thorek, Chicago

I am rather surprised that the important problem I submitted and which is dwelt upon in this number of Clinical Medicine and Surgery, has met with such meagre response. However, the thorough discussion of Dr. J. R. Sturre, of Minneapolis, is worth a great deal to anyone who is interested in this obscure question. After a painstaking analysis by Dr. Sturre and Dr. J. R. Smith, of Warsaw, Missouri, both arrive at the definite diagnosis of acute appendicitis. My diagnosis upon the patient's admission to the American Hospital also was acute appendicitis. My associates at the Hospital, my assistants, and everyone to whom the problem was presented, either immediately or after due reflection, made the diagnosis of acute appendicitis, with or without perforation.

Let me analyze the differential diagnostic points: Dr. Sturre has given a list which I shall not repeat. If you will read his discussion you will at once realize that he takes almost every possibility into consideration. There are a few things, however, that he did not include in his differential diagnosis, and in order to make the list complete I wish to add the following:

In the *first* place, in acute abdominal conditions, one should always make a thorough examination of the chest to eliminate *pleuro-pulmonary conditions, endo-myo-pericardial conditions,* and so on, all of which may give rise to a toxemia which, as is well known, may cause *peritonitism* (not peritonitis, but peritonitism—toxic irritation of the peritoneum), and thus simulate grave intra-abdominal mischief.

Second, an impacted stone in the right ureter will surely mimic acute appendicitis.

Third, pathologic conditions in the kidney and ureter, or perhaps a kink (Deitl's crisis) are entities to be seriously considered.

Fourth, prostatic abscess and diseases of the male adnexae—seminal vesiculitis, etc.—may give rise to confusing sypmtoms.

Fifth, pathologic conditions in the thoracic or lumbar spine, involving the nervous mechanism which supplies the abdominal muscles, etc., particularly if that osseous disease is resting upon an infectious basis (acute osteomyelitis and so on) should also be remembered.

Sixth, if the patient is a woman, of course, adnexal disease must be borne in mind; but in this instance, the patient being a male, we were relieved from that consideration.

Seventh, acute gastroenteritis, of any type, might successfully mimic the picture presented in this case.

Eighth, latent ileocecal tuberculosis, with

Fig. 1.—Complete volvulus of the entire great omentum.

an acute exacerbation, and possibly perforation, akin to the condition seen in typhoid, should be considered.

Lastly, the tragic perforation of unsuspected ulcers of other than tuberculous origin is well worth keeping in mind.

After considering all these factors in the case presented, operative interference was decided upon and operation was performed, after such preparation as the patient's general condition permitted.

Now, the important query: Did I find acute perforative appendicitis, or any of the conditions enumerated above, to be the cause of the symptoms?

Answer, *no*. We were all wrong in the diagnosis.

What were the findings? Upon opening the abdominal cavity a rather large quantity of serosanguineous fluid issued. I at once reached the suspected area, and lo and behold, a perfectly normal appendix came into view! The *great omentum*, however, in its lower half, was dark brown, much congested and swollen, while the upper half was black and gangrenous. It was suspended by a cord-like twist of tissue, the size and thickness of a thumb, giving the appearance of an umbilical cord. Upon investigation it was found that we were dealing with a volvulus of the great omentum, that had twisted upon its own axis four or five times, shutting off its own circulation and resulting in gangrene. (Fig. I). Upon closer inspection (Fig. II) the omental tissues appeared to be necrosed in many areas, and the larger vessels leading to the pedicle were thrombosed, thickened and more tortuous than usual.

I proceeded at once to remove the entire omentum, and this was accomplished in a very simple manner. A couple of strong Kocher artery forceps crushed the umbilical-cord-like, twisted portion of the omentum, close to the transverse colon, and it was removed.. After ligating the stumps, a thorough inspection was made of the accessible abdominal viscera, but disclosed nothing that would account for the occurrence of this unusual condition. The abdomen was closed, with a cigarette drain inserted in the lower angle of the wound to carry off the accumulated serosanguineous fluid.

The patient remained in bed under the usual postoperative care for a fortnight, and then left the hospital in excellent physical condition. At present, some months after the operation, he is back at work and apparently none the worse for his rather unusual experience.

Fig. 2.—Closer view of the gangrenous omentum.

In looking over the literature the number of cases of the type described here is rather small, and it is noteworthy that, prior to the operative interference, none of these cases were diagnosed correctly; so it appears that neither Dr. Sturre, Dr. Smith nor myself are such bad diagnosticians after all. With the number of intra-abdominal conditions that may present a similar symptomatology one must be a superdiagnostician—if such a term is permissible—to diagnose such a case correctly. However, the possibility of such an occurrence must be kept in mind, and I, for one, shall not forget, whenever I am confronted with a similar case, to recall this instructive experience.

Problem No. 11 (Surgical)

Presented by Dr. Max Thorek, Chicago

A boy, aged 10, who was admitted to the American Hospital on July 22, 1928, gave the following history:

Chief Complaint: Pain and swelling of the lower third of left leg and foot.

He had been well until about one week previous to his admission, when he suddenly complained of sharp, shooting pain in the left leg and foot. The pain became gradually worse and was accompanied by a slight swelling. There was no history of trauma.

Previous History: Measles and parotitis three years ago; acute bronchitis four years ago. Tonsils and adenoids were removed three years ago.

Family History: His father died of pneumonia. His mother, eight brothers and six sisters are living and well.

Physical Examination on Admission: Temperature 102°F., pulse 110, respirations 24.

The *left foot* appeared swollen, the swelling extending to the lower third of the leg. The skin over this area was tight and glistening but not reddened. No definite evidence of fluctuation could be made out. Physical examination otherwise negative.

Laboratory Findings: The *urine* showed a trace of albumin, a few casts and a trace of acetone and diacetic acid.

Blood: Leukocytes 16,000; polymorphonuclears 88 percent.

The patient was placed on symptomatic treatment. Hot compresses were applied, and a fracture box.

July 23, 1928: Incision above the ankle joint. No free pus was found. Smear showed staphylococci. A skiagram was absolutely negative.

Following this incision, the patient developed considerable pain, and the temperature fluctuated between 99° and 103°F., with the pulse around 120.

July 28, 1928: A bilateral incision was made posterior to the ankle joint, and a median incision over the instep. Large quantities of free pus were found and free drainage was established.

At this time the skiagram showed beginning inflammatory change in the bones in the region of the ankle.

This second operation did not afford the patient relief; the pain became more severe, the temperature remained around 102°F., and although there was free drainage the swelling did not subside.

August 6, 1928: The incision was repeated and pus evacuated.

The skiagram on this date showed early osteomyelitis of the lower tibia and the bones of the ankle joint.

There was no *marked* change in the general condition, the temperature or the subjective complaints. Hot compresses apparently did not relieve the pain or swelling, although there was considerable discharge.

August 17, 1928: The skiagram showed *marked extension* of the acute osteomyelitic process, upward and downward, in the bones of the ankle joint.

The compresses and immobilization were continued. The temperature continued to fluctuate between 99° and 102°F., and the pulse remained around 120. The patient continued to complain of severe pain, inability to move the ankle joint, marked swelling and tenderness. There was moderate drainage from the multiple incisions. The leukocyte count remained about the same—17,000.

The patient was kept under digitalis, protonuclein, strychnine, free elimination and irrigations with Dakin's solution, without marked change in the condition.

During the last week the temperature has dropped to normal, but the pulse rate remains persistently high (120). The x-ray findings are as before.

Requirement: What shall be done?

CLINICAL NOTES AND PRACTICAL SUGGESTIONS

Colloidal Metallic Supplies in Experimental Rabbit Syphilis

(A Therapeutic Suggestion)

FEW reports have been made upon the effects of colloidal solutions of the heavy metals or their salts in experimental syphilis.

Carefully controlled experiments have been made with **colloidal mercury sulphide-Hille,** colloidal bismuth sulphide and sulpharsenite, colloidal copper sulphide and sulpharsenite and Mervenol (colloidal mercury-copper sulphide) in experimental rabbit syphilis and the results will be reported in full detail at an early date.

The toxicity of these products has been carefully worked out and reported (see *Am. Journ. Syph.*, July, 1928, and CLIN. MED. AND SURG., Aug., 1928, p. 606).

The various preparations listed were administered intravenously, in safe dosage, to rabbits which had been inoculated with the spirochetes of syphilis and had developed the typical lesions and serologic reactions, and observations were made of the time required to clear up the four criteria of diagnosis—chancre, orchitis and positive blood Wassermann and Kahn reactions. Untreated control animals were run parallel, for comparison. The animals were observed for relapses of generalized syphilis for four months after the clearing up of the diagnostic criteria, and lymph node transfers were then made into other rabbits, to determine whether the treated animals were sterilized of spirochetes.

The maximum tolerated dose of colloidal mercury sulphide-Hille (30 mgm. per kilo of body weight), given intravenously to a rabbit, 24 hours after the intratesticular inoculation of *Spirochaetae pallida*, afforded complete protection against the development of syphilis.

These experiments, which were painstakingly checked at every point, lead to the following conclusions:

1.—Colloidal mercury sulphide-Hille, in the dosages employed, possesses excellent healing and definite sterilizing properties in experimental rabbit syphilis. Its potency in experimental rabbit syphilis is superior to that of other known mercurials.

2.—Colloidal bismuth sulphide, in a range of one-half of its maximum tolerated dose, is an effective healing agent but an ineffectual sterilizing agent in actively syphilitic rabbits. As an antiluetic, colloidal bismuth sulphide is inferior to potassium-bismuth tartrate.

3.—The maximum tolerated dose of colloidal bismuth sulpharsenite is without effect in the prophylaxis of experimental rabbit syphilis.

4.—Colloidal copper sulphide, at the dosages cited, is devoid of therapeutic activity in actively syphilitic rabbits.

5.—Colloidal copper sulpharsenite, in the amounts employed, possesses a slight healing action but no sterilizing activity in syphilitic rabbits.

6.—The therapeutic activity of Mervenol in experimental rabbit syphilis very probably resides wholly in its colloidal mercury sulphide-Hille component.

7.—The protective colloid solution employed to stabilize the colloidal heavy metal salts is entirely without antisyphilitic properties for rabbits.

8.—All of the colloids investigated are without deleterious effects upon the tissues at the site of intravenous administration and are apparently free from properties responsible for the production of anaphylaxis in rabbits.

9.—Because of its low toxicity and its very effective healing action and definite sterilizing properties in experimental rabbit syphilis, colloidal mercury sulphide-Hille should receive an adequate experimental study in the therapeusis of syphilis in man.

G. EARLE WAKERLIN, Ph.D., M.D.
Dept. of Physiology,
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Shoe-Dye Poisoning
(A Case Report)

A BOY, 9 years old, normal in all respects, went to the shoemaker, to have his shoes dyed, and got some of the dye on his hands when putting on his shoes.

He walked to his home, half a mile away, but said he felt somewhat weak and thought he was going to fall several times. He was rather frightened about his condition, as he had slight headache and precordial pain.

About 4 hours after contact with the dye, he suddenly developed cyanotic pallor, was nauseated and vomited several times within 6 hours.

Examination: Temperature, 99.4°F.; pulse 120, paradoxic (weaker during inspiration) indistinct, systolic murmur, heard best over the xiphoid, and venous murmur over right jugular vein.

Within 8 or 10 hours after the onset of the symptoms, the pallor, cyanosis and heart murmur disappeared; the pulse and temperature returned to normal and the child felt comfortable.

On July 26, the patient felt chilly, and this was followed by a feeling of heat and fatigue. On this date his *urine* showed some albumin; sp. grav. 1018; acid reaction. He urinated frequently and had a desire to defecate, but was unable to do so. These symptoms passed off within 24 hours, and he now appears to be well.

Could the shoe dye have caused such a condition?

J. J. BUNN, M.D.
Mt. Pleasant, No. Carolina.

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[This looks like an undoubted case of shoe-dye poisoning. Several such cases have been reported, and a study of them, by Dr. Muehlberger, appeared in J.A.M.A. for June 27, 1925 (abstracted in CLIN. MED., August, 1925, page 572.) The poisonous substance seems to be anilin or nitrobenzene, used as solvents of the dye. The principal symptoms noted in these reports were: cyanosis, vertigo, headache, weakness and nausea. The only treatment recommended was to remove the dye and keep the patient warm in bed.—ED.]

Give Diphtheria Antitoxin on Suspicion

ON PAGE 427 of the June, 1928, number of CLINICAL MEDICINE AND SURGERY, Dr. E. W. Reeves asks for information. In his case there is but little information given on which to base an opinion for differential diagnosis, but the case brings vividly to my mind a case I was called in consultation to see and treat.

Young man, age 22, previous health good. The afternoon before our night call, the doctor in charge was passing on his rounds and was called in to see the boy, who had a slight tonsillar infection, and gave treatment for the condition.

About 2 o'clock that night the doctor was called to come post haste and bring another physician with him, as the boy was choking from a badly swollen tongue. The doctor called me and we left in his car as quickly as we could get ready. On arriving, we found the young man with rapid, labored respiration and heart action; temperature, 104.5°F.; and his tongue protruding fully 1½ inches from his mouth and filling the vault so full that a speculum or tongue depressor was of no use.

After a hasty consultation we decided that if life was to be saved at all, diphtheria antitoxin was our only hope, and as I had it in my satchel we at once gave him 20,000 units, followed by a high enema (with a rectal tube) of 2 quarts of hot water and a "*handful*" of magnesium sulphate, while lying on the right side. This was retained for several hours, but in ½ hour after administering the antitoxin and the enema the young man began improving, in breathing and heart action. By 6 A.M., his bowels were flushed out thoroughly of a large amount of foul, septic material and all the other symptoms were improving. At 7 A.M. we gave 10,000 units more of diphtheria antitoxin and departed for home, and from this time on recovery was slow but complete.

In this case of Dr. Reeves, regardless of what the symptoms and diagnosis might have been, with the septic infection which certainly was present, I should not have

hesitated to give him 5,000 units of diphtheria antitoxin and repeat it in 12 hours, if needed; clean the lower bowel out with a high enema of hot magnesium sulphate solution; and treat the other symptoms as they were present.

I have used 3,000 to 5,000 units of diphtheria antitoxin *many* times in these aggravated, septic sore throats and have *always* been rewarded with the best of results. It may not be a true diphtheria case, but when the patients improve after the use of antitoxin, the proof is sufficient to justify one in using it.

J. R. SMITH, M.D.

Warsaw, Mo.

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[Horse serum, as contained in diphtheria antitoxin, is a foreign protein; and foreign proteins have made an enviable record in the treatment of infections. Perhaps they produce some profound changes in the body chemistry; perhaps they merely increase the number and activity of the leukocytes; in any case, *they work*.

It is possible that the antitoxin given in this case (supposing it was not actually a case of diphtheria) acted merely as a foreign protein. Cases have been known in which the administration of antitoxin, for its specific curative effect, ameliorated or cured attacks of gonorrhea. Here the effect was probably that of a non-specific foreign protein.

We suggest that Dr. Smith and others try injecting nuclein solution or Lactigen (sterile, fat-free milk) in their cases of acute infections and report their results.—ED.]

Epidural Saline Injections for the Relief of Pain in Tabes*

PAIN is the earliest symptom of tabes dorsalis and is generally misinterpreted, according to its location, as intercostal neuralgia, sciatica, gall-stones, appendicitis, etc. Many needless operations have been performed for the relief of non-existent abdominal conditions, simulated by tabetic pains. A Wassermann test, on the blood and spinal fluid, should be made before all operations of election, in order to rule out possible tabes.

No spinal puncture, even for diagnosis, is an office procedure. The equilibrium of the spinal fluid pressure is upset. All patients for spinal puncture should be in a hospital, and should be kept in bed for from 6 to 48 hours (according to symptoms), following the operation.

It must be remembered that the tabetic pains are *spinal root pains*—shooting and extremely severe, and not relieved by any of the coal-tar analgesics. Formerly, the only help for them was morphine; and the administration of that drug is always dangerous, especially in chronic cases.

We now have an effective and harmless method for relieving these agonizing pains, by the epidural injection of 30 cc. of physiologic saline solution, in the sacral region, close to the cauda equina, but not into the spinal canal. Relief is prompt and lasts for about a week. The injection may be repeated as required, and supplemental injections of 2 cc. may be made in each parasacral foramen. The method of operation of this treatment is unknown, but clinical results are gratifying.

SIGMUND KRUMHOLTZ, M.D.

Chicago, Ill.

*Abstract (by G.B.L.) of a clinical lecture before the Staff of the American Hospital, May 31, 1928.

The Wassermann Reaction

THE popular impression among the laity is that the "blood test" for syphilis is infallible.

In the case of neurasthenic patients, especially those with syphilophobia, the taking of a Wassermann test may prove calamitous. Even with a negative history and no signs of syphilis, if the Wassermann test is positive, these patients are so impressed that no amount of reasoning will disabuse them of the idea that they have the disease.

A young man once consulted me regarding a few harmless fibrous nodules in the skin of his arm. Later, he showed them to a young medical enthusiast who called for a Wassermann test, which proved positive, and for the next six months this man and his healthy wife both received arsphenamine and mercury injections. Needless to say the nodules remained unchanged.

Patches of psoriasis on the elbows and knees are often mistaken for a luetic eruption, and if the Wassermann reaction is positive, these patients are subjected to prolonged and useless anti-syphilitic treatment.

In 1925 a patient of mine informed me that he had had a syphilitic chancre twenty years previously that he had taken treatment at the time and had not noticed any symp-

toms since, but wanted a blood test to see if he was free from the disease. The Wassermann test was negative.

In the latter part of 1926 this man began to develop a certain amount of ataxia, was unable to step off or on a slowly moving street car, could not run, and had some difficulty in ordinary walking.. Disregarding the negative Wassermann test, he was given four courses of sulpharsphenamine, four grams to each course, with an interval of six weeks between courses, during which he had mercurial inunctions. The ataxia completely disapeared.

His wife, who had never exhibited any primary or secondary signs, had a serpiginous ulcer of the skin over the left scapula. Her Wassermann reaction was negative. She received the same treatment as her husband, and after the second dose this ulcer, which had existed for a couple of years, had entirely healed.

The negative Wassermann test may do as much harm as the ones which are suspiciously positive.

It has been said that the majority of syphilitic patients, today, are not being treated for syphilis, but for a positive Wassermann reaction. Even a four plus Wassermann reaction should not be accepted as diagnostic of syphilis, unless it is confirmed by clinical evidence or a definite history of infection.

Dr. Stokes, suggested as the greatest living authority on syphilis, says. "The Wassermann reaction is, not only susceptible to error in its performance, but also in its interpretation." If the symptoms and physical signs point to syphilis, then a positive Wassermann test merely confirms what you already know; and if negative, it conveys no information whatever.

R. STEWART MACARTHUR, M.D., C.M.
Los Angeles, Cal.

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[This warning is timely. The advent of serologic tests for syphilitic infection has well-nigh ruined the diagnostic acumen and medical judgment of many of the younger physicians.

Our medical forefathers were diagnosing and treating syphilis, with a fair degree of success, before the time of Wassermann and Ehrlich; and we, today, should be able to make a diagnosis of syphilis from the carefully taken history and the physical examination, using the Wassermann test as merely *confirmatory* evidence.

This emphasizes the fact that a laboratory cannot make a diagnosis. That can be done only by a *trained physician*, using the laboratory as a valuable helper in confirming the findings of his clinical examination.

The possibilities of error in the performance and interpretation of Wassermann reactions should be constantly borne in mind.—ED.]

A Correction

THE excellent article, "Physical Therapy and the Problem of Medical Cults and Isms", which appeared in the September number of CLIN. MED. AND SURG., on page 675, was written by Dr. Samuel J. Rose, of Lexington, Kentucky.

Through an error, which we deeply regret, his name was given as J. S. Rose.

Calcium Lactate in Varicose Ulcers
(A Case Report)

A PATIENT of mine—a woman of 50 years—had an ulcer, which had persisted for three years or more, on the lower part of her leg. I used a variety of recognized methods of treatment, but without any satisfactory results.

Finally I tried dressing the ulcer with powdered calcium lactate, renewing the dressing daily, and was gratified to see the discharge become less, the tissues assume a healthier appearance and the skin begin to grow from the margins. The ulcer is now almost entirely healed and the patient feels better than she has felt for a year.

I am also giving her the calcium lactate by mouth, 20 grains (1.325 Gm.) after each meal.

L. H. HENLEY, M.D.
Claremore, Okla.

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[The use of calcium in the treatment of chronic leg ulcers has a sound basis of support. The calcium content of the blood of many of these patients has been found to be low, and the oral administration of calcium lactate, with or without *parathyroid* extract, has been reported as producing favorable effects. Ultraviolet rays, probably because of their power to fix calcium in the tissues, have also been highly recommended in this condition.

When calcium lactate is to be given by mouth, it has been found to act best when combined with sugar of milk (as in Cal-

cilact) and administered when the stomach is *empty* (½ to 1 hour *before* meals).

If others try this method of treatment, we shall be glad to hear what results are obtained.—ED.]

The Osler Club

(A Letter from Europe)

ONE of the most interesting occasions I have attended was the meeting of the Osler Club, an account of which, taken from the *British Medical Journal*, I enclose.

"The anniversary of the birthday of Sir William Osler was celebratel in London on July 12th by the Osler Club. This club, which was founded in his memory and under the inspiration of his writings, in April last, for the study of the history of medicine, entertained a number of guests at an informal meeting.

"A reproduction of the Sargent crayon sketch of Sir William Osler, lent by the Royal Society of Medicine, occupied the place of honor, and through the kindness of several London librarians pictures of the triumvirate of British Medicine—Linacre, Harvey, and Sydenham—were displayed, together wtih some of Osler's favorite books—*Religio Medici*, the *Anatomy of Melancholy*, *Lettres de Gui Patin*, and works by the Swiss Osler, Conrad Gesner.

"Sir Wilmot Herringham, delivering the first Oslerian Oration, spoke of Osler's love of rare cases, not because they represented extremes of normal physiology, but because their rarity appealed to him as an artist. He told how the young Osler, inspired by the German educational 'system' and by what he had seen of practical training here, completely altered the outlook of medical teaching in America, how later he was responsible for the establishment of clinical units in this country, and of his part in the launching of the *Quarterly Journal of Medicine*. Dwelling happily on Osler's personal charm and affectionate nature, Sir Wilmot Herringham closed a speech notable for its genuine feeling and its dignified simplicity.

"Dr. Meynen, representing the German Ambassador, in proposing a vote of thanks, wished particular success to a club, one of whose aims was the promotion of international goodwill, and the name of whose patron saint was held in such reverent esteem in Germany.

"Sir Humphrey Rolleston pronounced his Oslerian Eulogy on 'Osler as a human being.' It was, he said, the combination of so many different personalities in one body that made Osler the beloved man that he was. No report could do justice to the charm of the eulogy, the final words of which summed up the spirit of the whole evening—'We shall never look upon the like of such a man again.'"

By the courtesy of the secretary and one of the founders, Mr. Alfred W. Franklin, I was present at this meeting held on Osler's birthday.

This club is especially devoted to the study of medical history, and already they have a most interesting collection of books, pictures and other articles of great historical interest.

It was extremely interesting to hear the reminiscences of these men who were, most of them, close friends of Osler during his life. You will see from this report that the meeting was rather widely representative. You will notice there were three of us from the States and one from Canada.

It seems to me, as I took occasion to say to them, that this club may have a wider significance and perhaps a greater function than was at first thought of. Whether by chance or design, they have organized to honor the one man who belonged equally to three great English-speaking nations: Canada, the United States and England. We have an equal pride in his work and it seems to me entirely possible that the Osler Club will contribute materially toward bringing the medical profession of these three countries into closer acquaintance. I have had only one week in England, but I am going back for a month and hope to do a little bit myself toward this highly desirable better acquaintance.

We think we are pretty good hosts in America, when we cut loose, but we will have to go fast to equal the hospitality of these British boys. Philip Franklin, who is amalgamated British-American, had shown me two major operations and had me to dinner in his home before I had been in London twenty-four hours. Arthur Hurst came up to London from Windsor on Sunday evening and kept a number of his friends away from vesper service to give me a supper at the Athenaeum, and Gill-Carey neglected his patients a whole afternoon to take me to lunch—or, excuse me, lunch-*eon*. They have arranged three meetings for me in September, so I suppose I'll come home for rest.

I'm seeing things in Paris now and shall probably go to Vienna next week.

BURTON HASELTINE, M.D.

Chicago, Ill.

THE LEISURE HOUR

October

This is neither the alpha nor the omega of the year; yet October is an important month and must be reckoned with.

At this time the farmer makes practically his last clean up of crops—apples, potatoes, cabbages, etc. The city man begins looking after his winter coal; screen doors and windows are "parked"; and cold weather lubrication for his automobile takes the place of summer grades of oil.

Even the schoolboy lays aside his hot-weather types of recreation. Bathing suits, marbles, kites, etc., are no longer in order and he begins to plan for the more appropriate cold-weather sports. So, when the recess bell rings this month, it finds him at a hardier type of play—"pom-pom-pullaway", tag; or perhaps the first crop of nuts attracts his attention.

Likewise must the doctor utilize this month as the time to scan his requirements for the colder days to come. Put your pet sunstroke remedy and your favorite prescription for greenapple colic on the top shelf.

October has its recreational advantages for the doctor, the same as it has for the schoolboy. Of course, we hardly expect to go nutting and get our fingers all covered with butternut stains (though that is not impossible), yet we should be getting all the pleasure out of life that this glorious month affords. Remember, the busiest doctor is always the one who has the most time to play.

FRANCIS N. RICHARDSON, M.D.,
Cleveland, Ohio.

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[We are glad to publish this bit of autumn philosophy and will be equally glad to publish brief notes from other readers, particularly in connection with their hobbies. We cannot, of course, use a great deal, but send the stuff along and we will print what we can and return the rest with our thanks and good wishes. Let's go!—ED.]

A Frightful Sound

The Englishman sat suddenly bolt upright. "My word!" he gasped, "W'at was that?"

"It's an owl," answered the guide.

"Yes, I know jolly well it was an 'owl," returned the Briton; "But w'at in 'eaven's name was 'owlin'?"—*Science News Letter*

The Laity

"What is the meaning of the word 'laity'?" Buck Kilby asked yesterday. "Well," said Eph Wiley, "the laity comprise those who take the medicine and those who undergo the operations." —*Topeka Capitol.*

Tricked Herself

Actress: "I'm ruined! I'm ruined! Look at this newspaper."

Friend: "Have they published some scandal about you?"

Actress: "Worse than that. I signed a testimonial stating that I always smoked Mildwhiff Cigarettes because they never bothered my throat; and I signed another testimonial that I always use Lymphatic Lozenges to protect my throat after smoking; and here they are, both on the same page!"—*Life.*

Unable to Judge

"It—er—seems," said he, regarding the unfortunate patient with scientific interest, "that the attacks of fever and chills appear on alternate days. Do you think—is it your opinion—that they have, so to speak, decreased in violence, if I may use that word?"

The patient smiled feebly.

"Doc," said he, "on fever days my head's so hot I can't think, and on ague days I shake so I can't hold an opinion."—*New York Globe.*

Thumbnail Therapeutics

Manganese Butyrate in Breast Infections

In breast infections, one ampule of manganese butyrate solution is injected deeply into the buttock, the breast is supported by a hammock binder and moist heat is applied for a period of 8 hours, during which time divided doses of calomel are also given, followed, in time, by a saline. At the end of the 8 hours, ice bags replace the heat applied to the breast and are kept on until general and local symptoms of inflammation disappear.—Drs. E. Cary and A. K. Van Dusen, in *Illinois M. J.*, October, 1927.

Amidopyrine

Amidopyrine is one of our best analgesics. It acts in small doses and produces few untoward effects. The usual dose is 3 to 5 grains (0.2 to 0.3 Gm.) several times a day, as required. If this is not effective it may be combined with ½ grain (30 mgm.) of codeine phosphate or phenobarbital or both.—Dr. Bernard Fantus, in *Bull. Pharm.*

Sulpharsphenamine

Sulpharsphenamine is valuable in treating syphilis, especially where medication cannot be given intravenously. The usual dose is 0.6 Gm., intramuscularly. Reactions almost never occur.—Dr. F. M. Havens, in *Squibb Memo.*

Alway Inject Oils Intramuscularly

Whenever any drug which is dissolved or suspended in a vegetable or mineral oil is to be given parenterally, it should *always* be injected *intramuscularly*. If given hypodermically, the oil is not absorbed but remains in the subcutaneous tissues and tends to form tumors. It is even more dangerous if given intravenously, as the oil droplets are very likely to cause coronary or cerebral embolism and death.

Be sure your needle is not in a vein when injecting oily preparations.

Intravenous Injections Through the Penis

When the subcutaneous veins are inaccessible it is possible to introduce solutions or transfused blood into the circulation through the venous spaces of the penis. A syringe or pump should be used.

Hold the penis on slight tension; introduce the needle through the skin and the tough tunica albuginea, 1 cm. lateral to the midline; inject a few cc. of isotonic salt solution to be sure that the needle is in place; inject the solution (citrated blood, physiologic salt or 10-percent dextrose) in the usual way.

This is not a method of choice but offers an "available vein" in an emergency.—Dr. E. Clay Shaw, in *J.A.M.A.*, Feb. 11, 1928.

Strontium Lactate in Tetany

Continuous oral administration of strontium lactate prevents the development of tetany in thyroparathyroidectomized dogs; such dogs adapt themselves to the loss of the parathyroids and recover. — W. W. Swingle and W. F. Wenner, in *Am. J. Physiol.*, Jan., 1926.

Mercurochrome-220, Soluble

Treatment with mercurochrome must still be considered in the experimental stage. Owing to its dangers it should be reserved for desperate cases of septicemia and other infections.—Dr. Davis, in *Am. J.M. Sc.*, Sept., 1926.

Tartar Emetic, Intravenously in Chancroid

In a number of cases of chancroid, excellent results have followed 4 to 8 intravenous injections of a sterile, 1-percent solution of antimony-potassium tartrate. The initial dose is 5 cc., increasing by 1 cc. at

each injection, up to a maximum of 12 cc. Intervals between injections, 1 to 5 days. No ill effects have been observed. — DR. HERMAN GOODMAN, in *J. Urol.*, April, 1925.

Iron Cacodylate in Post-Arsphenamine Anemia

In the anemia which frequently occurs during the course of the arsphenamine treatment of syphilis, the administration of intravenous injections of cacodylate of iron, 1 grain (65 mgm.) in 5 cc. of solution, at 5-day intervals—a total of 10 or more injections—generally restores the blood picture to normal. — DR. LOUIS STERN, in *New York M. J.*, Jan. 16, 1924.

Sodium Thiosulphate in Arsphenamine Poisoning

Sodium thiosulphate is known to be a detoxicant in heavy metal poisoning. In a case of persistent arsphenamine nephrosis, following the use of the drug for presumed congenital syphilis, the administration of 15 grains (1.0 Gm.) of thiosulphate, three times daily, by mouth, for two months, caused the urine to become normal. Perhaps more rapid improvement might have occurred in this case had the drug been given intravenously.—DR. ED. J. STIEGLITZ, Chicago, in *Illinois M. J.*, Oct., 1927.

Acriflavine Solutions

The best solvent for neutral acriflavine for intravenous therapy is not known. Tap water, because it is more likely to be alkaline, may be a better solvent than distilled water. We believe a buffered physiologic saline solution, made from an alkaline tap water, to be more desirable than physiologic saline made from distilled water.—DRS. V. BURKE and E. A. RODIER, Pullman, Wash, in *J. Lab. & Clin. Med.*, Dec., 1927.

Sodium or Potassium, Intravenously

1.—Potassium salts are far more toxic intravenously than the corresponding sodium salts.

2.—The action of a drug intravenously must be carefully studied; it cannot be inferred invariably from its action when administered by mouth.

3.—When the effect of the iodide radical is desired, sodium iodide, rather than potassium iodide, should be used intravenously. When the potassium effect is desired, potassium iodide is naturally chosen. In that event the dosage must be carefully regulated.—DAVID LOESER and A. L. KONWISER, in *J. Lab. & Clin. Med.*, March, 1924.

Intracutaneous Injections of Epinephrin

From observations made on children, free from cardiac or other circulatory or kidney diseases, it was found that the intracutaneous injection of epinephrin is usually followed promptly by the systemic effects of the drug. The action is much more pronounced than with the same quantity administered subcutaneously, and is probably somewhat greater than that obtained by intramuscular administration.—DR. J. D. PILCHER, Cleveland, O., in *J. Lab. & Clin. Med.*, Dec., 1927.

Calcium Lactate in Nervous Disorders

Twenty grains (1.3 Gms.) of calcium lactate were given four times daily to each of 18 patients suffering from nervous troubles. The medication was kept up for from 3 to 6 months. The results were quite uniform. In less than 48 hours there was a feeling of well-being, nervousness and fatigue disappeared and appetite and sleep improved. Four patients who had previously suffered from occipital headaches had no recurrence while on calcium medication. — DR. C. D. GAULT, in *Minnesota Med.*, Dec., 1927.

Sulpharsphenamine for Warts

Doses of sulpharsphenamine averaging 0.4 Gm., dissolved in a small amount of water and injected into the gluteal muscles, cured 6 cases of obstinate warts. Each patient received but one injection. — DR. R. L. SUTTON, in *J.A.M.A.*, Oct. 2, 1926.

Acriflavine in Uterine Infections

In 50 cases of cervical metritis during pregnancy, several of acute cervicitis and one of metritis, local treatment with acriflavine proved effective.—DR. D. MARTINEZ OLASCIRAGA, in *Revist. Med. d. Uruguay*, Dec., 1927.

Iron in Anemia

In experimental work done with iron, in anemia, the best hemoglobin improvement resulted from the administration of ferric acetate, ferric albuminate, ferric chloride and ferric citrate. Less satisfactory results followed the use of ferric oxide, ferrous carbonate (Blaud's mass), ferrous sulphate, ferrous lactate and reduced iron. —Drs. Mitchell and Schmidt, in *J. Biol. Chem.*, Oct., 1926.

Hiccup Relieved by Amidopyrine

Surprising success has been attained with the use of pyramidon (amidopyrine) in hiccup. It should be given in large doses at the beginning of the attack in refractory cases, 5 to 8 grains (0.32 to 0.52 Gm.) Amidopyrine may also be administered as a prophylactic. Five 8-grain doses may be taken without detriment.—Dr. H. Schottmueller, in *Münch. Med. Wchnschr.*, April 5, 1927.

Synergic Action of Epinephrin and Ephedrine

Animal studies have shown that the potential energy of ephedrine is utilized to its maximum in the presence of a small dose of epinephrin. With larger doses of epinephrin the synergism is still apparent but more in duration than in intensity. With very large doses the actions are inverted.—Drs. L. Launoy and P. Nicolle, in *Presse méd.*, June 23, 1928.

Digitalis and Heart Block

A tendency to heart block may be aggravated by digitalis, which necessitates special care when giving the drug in the course of acute rheumatic infections.—Drs. Carr and Reddick, Dallas, Tex.

Bismuth in Syphilis

Bismuth is declared to be much less toxic than the arsphenamines and less toxic than mercury. It does not seem to damage the liver to the same extent as the arsphenamines, or the kidneys to the same extent as mercury, and rarely, if ever, is an injection of it followed by a Herxheimer reaction.

Bismuth kills the surface spirochetes and heals up the skin manifestations more rapidly than does mercury; there is less pain after its intramuscular administration, and it is followed by fewer signs of intolerance; it also has a more rapid action than mercury on the blood Wassermann and other tests.

The combination of arsenic and bismuth is, however, much more efficacious in neurosyphilis than arsenic and mercury.

It is important that in every case of syphilis in its earlier stages a combination of either arsenic and bismuth or arsenic and mercury should be given, and that this combination should be continued up to the point of tolerance, until both the clinical and the serologic manifestations are cleared up.—Dr. David Lees, in *Brit. M. J.*, Aug. 20, 1927.

Neoarsphenamine in Pulmonary Gangrene

Neoarsphenamine seems to have a specific action in pulmonary gangrene and many consider its intravenous administration a standard procedure, following surgical evacuation of the abscess cavity.—Dr. Petit de la Villeon, in *Bull. et Mém. Soc. de Chirurg. de Paris*, Dec. 2, 1927.

Small Doses of Salvarsan (Arsphenamine)

Fractional doses of salvarsan (arsphenamine) rarely prove satisfactory and the requisite amount should therefore be given in one dose.—Dr. F. W. Oelze, in *Dermat. Wchnschr.*, Dec. 3, 1927.

Synthetic Ephedrine

Ephetonine, a synthetically prepared ephedrine, has all the pharmacologic action of ephedrine and may be used for the same indications. While solutions of ephedrine are optically active, those of ephetonine are inactive.—Dr. H. Krietman, *Münch. med. Wchnschr.*, Feb. 4, 1927.

Injections of Distilled Water

Injection of distilled water modifies the metabolism of leukocytes in such a way that they burst and set free antigens which constitute a vaccine of the most highly autogenous type.

In a case of disturbed basal metabolism following gonorrheal infection, excellent results were obtained after two subcutaneous injections of 8 cc. of distilled water within a week. Such injections, if they do no good, never do harm.—Dr. G. A. Stephens, in *The Prescriber*, August, 1927.

Sodium Salicylate Intravenously

The following formula is the best medium for employing sodium salicylate as an intravenous injection without causing thrombosis or damage to the walls of the veins;

Sodium salicylate....15 grains (1 Gm.)
Glucose (30-percent solution in water) .....10 cc.

A 30-percent solution of glucose is the limit if the solution is to be easily sterilizable. The importance of sodium salicylate as an intravenous injection is mainly in the treatment of encephalitis lethargica. —Dr. G. Rosenthal, in *Prog. méd.* (Paris), Nov. 5, 1927.

Quinidine in Extrasystoles and Hypotension

The one drug which has regularly proved helpful in the treatment of cardiac extrasystoles is quinidine. Most of these patients have a low blood pressure and feel weak and listless on damp, cloudy days. The drug seems to improve this condition, also.—Dr. James J. Walsh, in *International Clinics*, Dec., 1927.

Contraindications to Cinchophen

The use of cinchophen is contraindicated in the presence of organic disease or temporary impairment of the kidneys or gastrointestinal system. It should be given with caution in hepatic disease, during pregnancy and convalescence from debilitating diseases and in drug and alcohol addicts.

Colloidal Bismuth in Syphilis

Apparently excellent results have been obtained in 11 cases of secondary and tertiary syphilis with the use of colloidal bismuth (Bismuthoidol). In general, the injections deep into the gluteal muscle were absolutely painless. In one case— an old and stubborn case of neurosyphilis— intravenous injection was tried but was abandoned owing to slight shock and dizziness having appeared, accompanied by flushing of the face which lasted about ten minutes. The dose of colloidal bismuth is 2 mg. per ampule of 2 cc. (3 injections weekly). Any increase in this quantity of metal is rapidly eliminated.—Dr. Abraham A. Levy, New York, in *Am. Med.*, March, 1928.

Intravenous Injections

When it is difficult to find a vein sufficiently large to receive an intravenous injection, have the patient immerse the hand and forearm, up to the elbow, in hot water for 15 minutes. By this method most patients will develop a vein sufficiently large to make the insertion of a needle easy.—Dr. F. B. Kirby, Evanston, Ill.

Calcium and Pregnancy

The combination of calcium lactate with sodium lactate is not only a means of administering calcium in a most convenient form but also of securing the important factor of calcium retention and calcium assimilation during pregnancy.—Dr. Oscar Loew, Munich, Germany, in *M. J. & Record*, Jan. 4, 1928.

Ephedrine in Adams-Stokes Syndrome

In the case of a woman aged 68 who was having an average of three attacks every ten minutes, one 0.05-Gram ephedrine capsule, by mouth, caused the attacks to cease within thirty minutes, and they did not recur for thirty-six hours. On taking one capsule each morning, the woman was completely freed from the attacks and could resume her household duties. After taking the drug for three weeks, it was withheld but the attacks recurred in forty-eight hours and ephedrine administration had to be resumed.—Dr. M. Hollingsworth, in *California and West. Med.*, June, 1927.

Calcium Chloride

If Calcium Chloride is to be injected, it must be given *intravenously* and *with great care*. If it enters the tissues it will cause ulceration.

Current Medical Literature

Tryparsamide in Neurosyphilis

Dr. T. C. C. Fong, of Washington, D. C., in *M. J. and Record*, July 18, 1928, states that tryparsamide has been used in St. Elizabeth's Hospital, for treating neurosyphilis, for nearly five years. Forty-eight patients have been so treated, including all types and stages of the disease.

The technic consists of ten weekly injections, the initial injection being 2 Gm. dissolved in 10 cc. of sterile distilled water, with subsequent injections of 3 Gm. A few patients received supplemental mercurial treatment; others received bismuth intramuscularly. The rest period between courses varies from 4 to 8 weeks.

In only 1 case was an eye complaint made on examination. Lesions of the optic nerve contraindicate tryparsamide treatment. Some of the patients treated have had as much as 200 to 300 Gm. of the drug without any evident detriment to their vision. Neither was local or general tissue irritation, to any untoward degree, observed.

Of the 48 cases treated, 44 were cases of general paresis, 1 taboparesis, and 3 cerebrospinal syphilis.

The results have shown 63.5 percent remissions, 27 percent of which may be classified as very good and 35.5 as partial; 22 percent were unimproved; deaths amounted to 12.5 percent, the majority being due to a terminal infection such as bronchopneumonia.

The improvements in cases of neurosyphilis treated by tryparsamide are mainly clinical. Neurologically and serologically the improvements are not parallel with the clinical results. The blood Wassermann test was improved in about 60 percent.

On the whole, the author considers the results have far surpassed those from anything hitherto employed, with the exception of malaria treatment. The use of the drug in neurosyphilis has proved far superior to the former standard methods of treatment.

Intraperitoneal Injections of Neoarsphenamine for Congenital Syphilis

In *Am. J. Dis. Child.*, Jan., 1928, Dr. C. G. Grulee and his associates say that the arsenical compounds will probably continue to give the most uniformly satisfactory results in the treatment of congenital syphilis. Administration of these compounds to the child is, however, difficult.

Experience covering a period of two years has led the authors to conclude that the intraperitoneal injection of neoarsphenamine is a rational therapeutic method of treating congenital syphilis.

The treatment usually consists of 4 injections, at 3-day intervals, followed by 4 injections at 7-day intervals, the same dose being used each time. The child is then observed for a month, when a Wassermann test is made and a roentgenogram taken.

Of 25 patients thus treated, 16 or 70 percent were pronounced clinically cured, and 4 more showed distinct clinical improvement, but these latter children did not complete the treatment. The death of one child during the treatment could be attributed to it.

New Light on the Principles of Chemotherapy

A paper by Sir Almoth E. Wright which will attract the universal attention of those who are interested in immunologic therapeutics is published in *Lancet*, Dec. 24, 1927.

Wright severely criticizes the looseness of Ehrlich's fundamental conceptions in regard to chemotherapy, especially in regard to the insufficiency of nomenclature. Ehrlich's doctrine is inadequate and in many respects erroneous; that is to say, Wright considers that Ehrlich's doctrines of *theraplia magna sterilisans* and *therapia sterilisans fractionata* are both unsound, principally because, while one part of infecting microbes circulates in the blood, or lies in regions to which there is ready access from the blood, yet another part lies in regions so physiologically remote that it might quite safely be postulated that chemotherapeutic agents cannot penetrate to them.

In his discussion, Wright shows that the efficacy of antibacterial treatment by pharmacochemical, bacteriotropic agents depends, not only upon their entering into *rapid* destructive chemical combination with the microbes and *exclusively* with these, but also upon the chemical agents in question being transported from the blood into the lymph and from the lymph into the secretory fluids of the organism. It appears that the failures of pharmaco-chemical —and the same holds good of immuno-chemical treatment—are seemingly more often imputable to a default of convection than to a default in the chemical constitution of the therapeutic agent employed.

Dealing with the question of how antibacterial elements which may be present in the circulating blood can be brought into operation upon infecting microbes in nonbacteriotropic envelopes or niduses, which ordinarily escape destruction, Wright calls this general procedure *kataphylaxis*. He finds, in general, that hypertonic salt solutions when injected into the blood act as powerful serogogues. In the case where the circulating blood contains chemotherapeutic

elements (immumo- as well as phramaco-therapeutic elements) the salt solutions will carry these in a rapid stream through the tissues, achieving very rapidly that transport of antibacterial elements into the foci of infection which will, even when it is favored by reduced blood coagulability, be accomplished only very slowly.

Wright's paper should be read *in extenso* by those interested, as many important sequential matters cannot be included in a brief abstract.

Acetarsone

According to an editorial in *J. Chemotherapy*, April, 1928 Stovarsol (acetarsone), an antisyphilitic remedy proposed by French syphilologists in 1922, is a pentavalent arsenical which contains 27 percent of arsenic. It has the advantage over arsphenamine and other arsenicals that it may be administered orally.

Clinical investigations, however, apparently justify the attitude of a large majority of syphilologists in not considering acetarsone equivalent to the arsphenamines in the treatment of syphilis, although it may be substituted for the latter under special conditions in which they cannot be employed.

There appear to be considerable grounds for the view that acetarsone *prevents* the development of syphilis, It should be prescribed soon after exposure, for 6 to 8 weeks, in courses of 5 to 7 doses (1 to 1.5 Gm. each), separated by rest periods of 3 days in the first stage of treatment and of 5 days in the later stage. After an interval of 3 to 4 weeks, the entire series of courses should be repeated. The Wassermann test should be repeatedly checked.

There is always the possibility, however, that this may lead to a latent infection.

Stovarsol is considered by many to be very suitable for administration to children.

In the same issue of *J. Chemotherapy* there are several abstracts of articles testifying to the excellent results obtained with sodium-stovarsol in cases of malaria; also of an article by Covey in *Nebraska S.M.J.*, June, 1927, in which Stovarsol proved to be an excellent remedy for both ameba and flagellate intestinal manifestations.

Physiochemotherapy of Neural Syphilis

The intelligent combination of all known measures often gives brilliant results in cases of syphilis, according to Dr. Curran Pope, in *Arch. Physical Therap., X-Ray, Radium*, Oct., 1927.

The essentials of the treatment include diet, rest, tonics, exercise, etc.; hydrotherapy, diathermy and galvanism used daily; administration of mercury, and bismuth, hypodermically, and of dextrose and the arsensicals, intravenously; and adjuvant measures, such as actinic radiations with the air-cooled lamp, static electricity, etc.

Twenty to 40 cc. of sterile dextrose solution are administered, intravenously, early in the morning, preceded by arsenate or arsphenamine, when prescribed. This combats the edema and localized acidosis which favor treponema growth.

Immediately following the dextrose injection, diathermy (300 to 500 or 600 milliamperes) is applied to the brain, cord or cerebrospinal roots, depending upon the localization of the disease. This is immediately followed by galvanism, dosage 10 to 15 milliamperes for five to ten minutes, applied in the same way as the diathermy, placing the active, negative electrode as near the site of lesion as possible and the positive electrode in such a position that the current will as nearly as possible pass directly through the involved tissue.

Galvanism is more efficient when preceded by diathermy and Pope believes that the medicaments introduced into the circulation are enhanced in their activity by the combined use of diathermy and galvanism.

The actinic, air-cooled lamp is used two or three times weekly, in markedly run down patients.

On four days of the week the diathermy-galvanism treatment is given without glucose or arsphenamine.

Arthritis

Arthritis has been known since ancient times, the Egyptians, Greeks and Romans being familiar with it. There has been comparatively small advance in successful treatment in modern times.

In *Northwest Medical* (Chicago), March, 1928, Dr. D. E. Markson reviews the etiology, classification and treatment of arthritis at length.

In the Northwestern University Clinics, Goldthwaite's classification is used, namely: (1) the infectious type; (2) the atrophic type, more usually affecting women; (3) the hypertrophic or senescent type, characterized by destruction of the cartilages of the larger joints.

Regarding etiology, many factors are invoked —the streptococcus (variety not agreed upon); focal infections, especially of the teeth or tonsils; intestinal toxemia; amebiasis; allergy; etc.

In the author's series of 81 cases of chronic infectious arthritis, foci of infection were found as follows: tonsils 26, teeth 25, teeth and tonsils combined 12; teeth, tonsils and other foci combined 63 percent; altogether, foci of infection were found in 71 percent of this series.

The view that there is a disturbed capillary-bed circulation in arthritis, with lowered sugar tolerance, was confirmed in only 25 percent of the author's cases.

The diagnosis of chronic arthritis presents little difficulty. A patient, under 35 years of age, complaining of pain in many joints, without fusiform swelling, ulnar deviation and intermetacarpal atrophy is a case of chronic infectious arthritis. A patient, over 35 years of age, well-nourished, complaining of pain in the larger joints, with or without Heberden's Nodes, is one of chronic hypertrophic arthritis.

In treatment, removal of foci of infection deserves the first consideration.

The use of hydro-electric therapeutic measures, heliotherapy, heat, electricity, x-ray, hydrotherapy, massage and exercise, is of definite value in a selected group of cases.

Specific vaccine treatment is of value, especially in cases of the chronic infectious type.

In the line of drugs, the author thinks that arsenic and iodides should be given to every patient. Arsenic can be administered in the form of Fowler's solution, by mouth. In selected

cases, the author uses neoarsphenamine, intravenously, as follows: weekly doses, beginning with 0.3 Gm. for two doses, 0.4 Gm. for two doses and 0.6 Gm. for two doses. The patient is given a rest period for two weeks, after which an additional six doses are given according to the plan outlined. Sulpharsphenamine, given intramuscularly, in the same routine, is preferred for old, arteriosclerotic patients.

Amiodoxyl benzoate has proved a valuable drug in the author's experience. In 32 patients (14 chronic infectious, 13 hypertrophic, 1 atrophic and 4 unclassified) in which the drug was slowly administered by gravity, the improvement following the first two injections was greater than that noted in subsequent injections. All of the 14 chronic infectious cases were relieved from pain, 6 being markedly improved, and in 2 cases the results were miraculous. The author feels that amiodoxyl is of definite benefit in this type of arthritis.

Tryparsamide in Paresis

Owing to its penetrability to deep-seated foci, tryparsamide is known to act very favorably in spirochetal infections of the central nervous system.

In a paper (soon to be published in *J. Nerv. and Ment. Dis.*) Drs. R. C. Jaenike and G. W. Forman, of the State Hospital, Osawatomie, Kansas, report their findings in a series of 100 frank paretics, treated by tryparsamide, over a period of three years. Mercury injections were given in conjunction. The 100 patients received an average of 34.6 injections of 3 Gm. each of tryparsamide. Five (5 percent) of these patients have been considered as cured; 38 (38 percent) showed improvement, both mentally and physically; 15 of these have left the Institution and are behaving normally; 2 (2 percent) patients have improved clinically but not mentally; 34 (34 percent) are either stationary or have declined.

The best results are in those patients whose symptoms were less than a year in duration at time of admission, and in those with the manic type of symptoms.

In 35 patients, the spinal gold chloride curve test was reduced from paretic to tabetic type; in 6 cases the curve became normal.

In 6 cases, subjective eye symptoms appeared and the treatment was discontinued.

Chemotherapy of Sulpharsphenamine and other Organic Arsenicals

In reviewing the work of the U. S. Hygienic Laboratory regarding the clinical use of organic arsenicals, Dr. Carl Voegtlin, in *Venereal Dis. Information*, Nov. 20, 1927, states that the intravenous injection of arsphenamine and neoarsphenamine has no other advantage over intramuscular or subcutaneous injection than to avoid extremely painful local reactions.

Research at the laboratory led to a method for the preparation of sulpharsphenamine and experiments demonstrated the fact that sulpharsphenamine is suitable for intramuscular injection and that its toxicity, trypanocidal and especially treponemicidal potency compare favorably with those of arsphenamine and neoarsphenamine. Clinical experience covering a period of five years has shown that sulpharsphenamine is a valuable addition to the list of arsphenamine derivatives. It is also well suited for subcutaneous injection into infants and for intramuscular injection into adults whose veins are not easily accessible, as in the obese. It appears to be better tolerated in cardiovascular cases and those having an idiosyncrasy for the other arsphenamines. It also has a place in the local treatment of Vincent's angina.

It is now a generally accepted conclusion that arsphenamine is not a directly active substance against syphilis, but that it has to undergo partial oxidation in the body before it is converted into an active modification. Directly active parasiticidal forms of arsphenamine are much more toxic for the host and differences in the rate of biologic oxidation of arsphenamine in different individuals probably account for the differences in toxicity of arsphenamine in different individuals.

Clinically, the arsphenamines are deficient in therapeutic action in cases of parenchymatous neurosyphilis. At the Hygienic Laboratory it was decided to inoculate the cerebrospinal fluid with a heavy suspension in blood of living trypanosomes and to test the effectiveness of intravenous injections of the different arsenicals, with respect to their power to kill off the parasites. The results indicated that tryparsamide is the most effective compound studied and that sulpharsphenamine has a fairly high effectiveness, whereas arsphenamine and neoarsphenamine occupy a lower position.

Trypaflavine (Neutral Acriflavine) in Gonorrhea

In *Urol. and Cutan. Rev.*, May, 1928, Dr. Josef Konrad, of Innsbruck, Austria, states, that, since January, 1927, 140 patients (110 men, 30 women) with gonorrhea were treated with trypaflavine (neutral acriflavine).

The intravenous employment of trypaflavine is to be recommended in all stages of gonorrhea among men and, combined with the other commonly employed treatment, leads to a decided shortening of the course of treatment. In all cases of acute posterior involvement, the use of trypaflavine (neutral acriflavine) solutions, in a strength of 1:2,000, in a Janet irrigation, in addition to the intravenous injection of 1/2 to 2 percent solutions, exercises a favorable influence upon the course of the disease. The appearance of any complication is very unusual.

In the treatment of gonorrhea in women, intravenous therapy, along with the ordinary treatment, is to be recommended, but the results are not so good as in men.

A Non-Boiling Method of Syringe Sterilization

To avoid the inconveniences of the boiling method of sterilizing syringes, Dr. I. L. Ohlman, of Pittsburgh, in *Urol. & Cutan. Rev.*, Dec., 1927, describes the following non-boiling method:

Three jars are prepared. Jar A contains a solution of cresol; Jar B contains 95-percent alcohol; Jar C contains commercial ether.

After office hours, syringes are washed in running water and dropped in Jar A, the pistons being removed. The next day, previous to use, the syringes are withdrawn with a sterile instrument forceps from Jar A and placed in Jar B. When about to be used, the syringe is withdrawn in the same way from Jar B and thoroughly washed in Jar C (a wide mouthed jar) by filling two or three times. Tests have shown that syringes treated in this way are completely sterile.

Sodium and Potassium in Arterial Hypertension

General available evidence is that calcium chloride produces an inorganic acidosis, with increased excretion of ammonia and soda; that potassium chloride, without change of the acid-alkali ratio, gives an increase of soda excretion; that potassium citrate produces an alkalosis, with an increased soda excretion; and that all three, with proper dosage, reduce arterial pressure in the large majority of cases of hypertension.

From clinical experiments, Dr. W. L. T. Addison, Toronto, in *Canad. M.A.J.*, March, 1928, finds that the giving of potassium chloride, bromide and citrate is associated with a drop in blood pressure, with a decrease in the symptoms of hypertension; and that the giving of sodium chloride and bromide is associated with a rise of blood pressure and an increase in the symptoms of hypertension.

In one case, the potassium citrate was as efficient in the reduction of blood pressure as was the chloride, and in other cases it was more efficient than the chloride.

Sodium Iodide Intravenously

In *Southern M. & S.*, Jan., 1928, Dr. Chas. B. Herman, of Statesville, N. C., discusses massive intravenous doses of sodium iodide. Experiments have shown that intravenous injections of hypotonic solutions increase intracranial pressure and brain bulk; hypertonic injections cause a decrease in brain bulk.

The method of preparing sodium iodide for intravenous injection by the author was that used by Dr. F. Farnell, of Providence, R. I.

One hundred cc. of freshly distilled water is autoclaved for 20 minutes; to this is added 155 grains (10.075 Gm.) of sodium iodide (if a 10 percent solution is to be used); the solution is then boiled for a minimum of 10 minutes, filtered through a sterile filter, cooled and administered immediately, by the gravity method. The average dose is 100 cc. which is repeated at 4- to 7-day intervals. A small dose (about 20 cc.) should be given at first to find if the patient is hypersensitive to the drug.

Among a number of cases being treated, one case of lethargic encephalitis of 3 years' standing, one case of encephalitis of similar duration and a case of atactic paraplegia are stated by the author to be much improved under intravenous therapy with massive doses of sodium iodide. This method of administration does not cause iodism.

The probable explanation is that cerebrospinal pressure in general is lowered by the hypertonic solution of sodium iodide, and the fluid contained in the tissue spaces of an edematous area, the perivascular drainage of which has been obstructed by cell infiltration, is absorbed back into the blood stream.

Gold Therapy of Psoriasis

In *Urol. & Cutan. Rev.*, Feb., 1928, Dr. N. Toomey, of St. Louis, states that since his previous report he has seen a case of acute recent psoriasis respond rapidly and admirably to the oral exhibition of the strong gold suspension made by the brominization process, without any other internal medication. He thinks that continuation of gold therapy, especially in acute psoriasis, is entirely justified by clinical evidence.

The strong gold suspension is prepared as follows:

Gold tribromide	2.44 Gm.
Bromine water	100.00 cc.

Place the gold tribromide in a clean procelain mortar or beaker or, still better, in a wide-mouthed, glass-stoppered shaking bottle; add part of the bromide water; stir with a glass rod. Add bromine water to make up the whole to nearly 110 cc.; stir and shake vigorously for several minutes. Then drive off the bromine by placing the container over a very, very slow fire until all odor of bromine has disappeared; this will require from fifteen to twenty minutes. Replace the water lost by evaporation by making the whole up to 100 cc. with distilled water. The suspension of gold should not come in contact with a metal.

Ephedrine in Leprosy

Drs. E. Muir and S. P. Chatterji, in *Indian Med. Gaz.*, Apr., 1928, state that they found Ephedrine much more efficacious than adrenalin (epinephrin) in relieving the nerve pains in leprosy.

Ephedrine is believed to act by causing contraction of the arterioles of the nerve trunks and reducing engorgement. A dose of 0.05 to 0.1 Gm. is sufficient, in most cases, to cause relief in from 45 to 72 minutes, and the relief lasts for 24 to 72 hours or longer. Opium and its derivatives give only a slight, short relief and have a harmful effect on the general condition of the patients.

Mercurochrome-Glucose Solution for Gonorrhea

Dr. W. M. Coppridge, of Durham, N. C., reports, in *Southern Med. & Surg.*, Sept., 1927, that in 30 cases of gonorrheal complications he used mercurochrome in glucose solution, which has been found very effective by others.

A 50-percent glucose solution is made, with double distilled water, and sterilized; then mercurochrome powder is added in proportions of 1 Gm. to 100 cc. of the sugar solution, thereby making a 1-percent mercurochrome in 50-percent glucose solution. The solution should not be more than 24 to 36 hours old when used.

A dose of 5 cc. is injected, intravenously, every second or third day, working the dose up to 15 cc. The average number of doses in any one case was five, and the largest number was nine. In only two cases were ill effects noted; one showing nausea and vomiting, the other a severe chill a few hours after injection.

Twenty-eight of the 30 cases treated represented gonorrheal complications of more than average severity. All were in males and prostatitis was present in every case. Other routine treatments were carried out in addition to the injections.

In every case the patient showed considerable improvement immediately after the treatment was started. Relief of pain and diminution of swelling were almost constant symptoms. Urinary symptoms improved and discharges were checked; but none of the cases can be reported as "cured". Marked improvement is the most that can be said at present.

Hexylresorcinol in Spinal Fluid

In order to test if hexylresorcinol, administered by mouth, might be eliminated through the cerebrospinal fluid, Dr. H. P. Schenck, of Philadelphia, examined a large series of cerebrospinal fluids obtained from patients to whom the drug had been orally administered.

In *Arch. Neurol. & Psychiat.*, Oct., 1927, Dr. Schenck states that the drug is probably eliminated in small amounts in the cerebrospinal fluid when administered orally; but is not obtained from the fluid in appreciable amounts when its administration has been for less than five days or in dosage of less than 15 grains daily.

The concentration of the drug in the cerebrospinal fluid under these conditions is less than 0.015 percent and is not sufficient to indicate a reduction of surface tension.

As a prophylactic in neurosurgery, hexylresorcinol may possess slight but doubtful value.

Protein Therapy of Syphilis

Drs. H. Gougerot and E. Peyre, in *Monde méd.*, Feb. 1, 1928, say that in syphilis there is a mixture of immunity and allergy. By certain tests it can be determined whether a syphilitic is allergic or anallergic, and from the prognostic and therapeutic viewpoints it is desirable that this should be determined.

The simplest test for allergy is that of Dujardin-Decamp. This consists of the daily intradermal injection of 0.2 cc. of protein (hemostyl —a horse serum preparation). If the syphilitic shows a positive reaction he is allergic and the prognosis is favorable.

If the reaction is negative the syphilitic is anallergic and it is necessary to sensitize him, either by specific antigens (such as injections of treponema extract) or non-specific antigens (proteins, serums, toxins, etc.) or indirectly by chemotherapeutic agents. The hemostyl protein test should be repeated weekly until it becomes positive.

In any case, every syphilitic should have a Dujardin-Decamp test every 6 or 12 months. If the subject gives a negative result he is still always a menace, despite any apparent cure, such as negative Wassermann reactions, normal cerebrospinal fluid, etc. But if the test is positive, the prognosis as regards therapeutic recovery is always favorable.

Substances which Stimulate Bile Secretion

An extensive pharmacodynamic study of stimulants of bile secretion, by Professor Mario Soto, published in *Semana méd.*, Buenos Aires, February 29, 1928, showed that the great majority of choleretic substances belong to the aromatic series.

All the organic acids of cyclic type which were tried proved to be choleretic, with the exception of the isophthalic acid.

The substitution of a carbon for the nitrogen radical in the cyclic nucleus, as in the case of phenyl-quinolin-carbonic acid, does not diminish its energetic choleretic action.

The increased quantity of bile resulting from the tested substances coincided with a decrease in its density and this phenomenon was observed to be more marked with salicylic acid.

The results of the author's experiments would appear to justify further investigation for the purpose of classifying groups of substances according to their functional choleretic properties.

Lead Treatment of Cancer

At the International Conference on Cancer, held at London, July, 1928, reported in *Lancet*, Aug. 4, 1928, the consensus of clinical opinion regarding the efficacy of the Blair Bell colloidal lead therapy of cancer was rather against this therapeutic method. In St. Bartholomew's Hospital, London, and in the London Cancer Hospital the reports, after a fair trial of the method, were distinctly unfavorable. On the other hand, some favorable results were observed in Birmingham, England, and in Paris, France.

The general conclusion reached by the Conference was to the effect that lead treatment of cancer had not yet reached the stage of practical therapeutics for the average physician, but that experimental work in this therapy should continue with a view to the discovery of a lead compound less toxic in its effects than those now used.

Dr. H. J. Ullman, Director of Cancer Research of the Santa Barbara Cottage Hospital, in *Radiol. Rev.*, July, 1928, states, that orthophosphate of lead had essentially the same effect on tumors as has colloidal lead and is much less toxic.

Atophan (Cinchophen) in Gout

In *Proc. Staff Meet. of Mayo Clinic*, Nov. 2, 1927, Dr. E. B. Rentschler deals with the treatment of gout.

Disturbance in purin metabolism is the dominant factor in the cause of gouty arthritis; heredity and purin-rich food and alcoholic excess are the chief inciting factors.

Treatment must be dietary as well as medicinal. Purin-free, high-protein foods have been demonstrated to be active in eliminating uric acid, but if the kidney is damaged the intake of protein must be restricted.

In all Dr. Rentschler's cases the medicament used was atophan (cinchophen). This is desirable because of its twofold action: it is analgesic and it increases elimination of uric acid. At the commencement of atophan (cinchophen) therapy it seems desirable to give alkalis for a brief period to prevent the deposition of urates, which might occur in acid urine, in the early stage of increased urate excretion. Heat applied to the affected part during treatment gives great comfort to the patient.

In the early stages of gout, when diagnosis is not obvious and there is no contributory evidence, a therapeutic test will often lead to a correct diagnosis.

Leukocyte Control

From animal experiments, Dr. W. J. R. Camp, Chicago, writing in *J. Lab. & Clin. Med.*, Dec., 1927, finds:

1.—The distribution of leukocytes in the peripheral circulating blood is controlled by the autonomic nervous system.

2.—The partition of leukocytes in the peripheral circulating blood is an index of autonomic balance, the lymphocytes running parallel to parasympathetic tone and the neutrophiles to sympathetic tone.

3.—The increase of neutrophiles takes place at the expense of the lymphocytes and the lymphocytes increase at the expense of the neutrophiles.

4.—With an increase in the sympathetic tone there occurs a concomitant decrease in the lymphocytes.

5.—With an increase in the parasympathetic tone there occurs a concomitant decrease in the neutrophiles.

6.—The spleen plays no part in the production of a drug leukocytosis.

7.—It is possible and probable that this influence of the autonomic system is mediated through the medium of inorganic ions, such as calcium.

The Skin as a Defense Organ in Syphilis

In *Venereal Dis. Information*, Nov. 20, 1927, E. Finger points out that, prior to the close of the eighteenth century, tertiary cutaneous syphilitic lesions were common but that general paralysis and tabes were rare. Since then the tertiary skin lesions have become rare but the nervous lesions have greatly increased.

When the skin tissues take up the defense against syphilis they tend to immunize the nervous system. When the nervous system takes up the defense there is a tendency to skin immunization.

The author ascribes the change in the clinical evolution of syphilis to the different modes of treatment. Formerly it was considered that the administration of remedies immediately after the appearance of the primary lesion would cause a severe course of the disease. Since 1906, the principle of early local treatment has been stressed.

Formerly, patients had severe tertiary cutaneous symptoms, and at present tabes, paralysis and aortitis, but no longer gummas, because the socalled preventive treatment has hindered formation of spirochete foci in the skin or energetic treatment in the early stages has destroyed them, while that has not been possible in the covering membranes of the nerves.

Iodine in the Treatment of Syphilis

The extensive employment of iodine in syphilis does not rest upon any determined scientific basis. In *J. Chemotherapy*, April, 1928, Drs. G. W. Raiziss and M. Severac describe animal experiments to determine the extent of the curative action of several iodine compounds in well-developed primary syphilis. The experiments led to these conclusions:

1.—If antisyphilitic medication is withheld from rabbits infected with *Spirochaeta pallida*, the lesions do not involute and the organisms do not disappear of themselves within at least 3 months after infection.

2.—In undertreated syphilitic animals, active spirochetes may be detected in the testicles for many weeks after the drug has been administered, while the time required for the genital organs to again assume a normal appearance is much longer.

3.—The oral administration of iodine in the form of potassium iodide, Peptoiodine or calcium iodothiourea results in the early disappearance of all syphilitic manifestations. Very large doses of these three iodine compounds; i.e., those closely approximating the maximum tolerated dose, induce a rapid clearing up of the visible evidences of the disease.

4.—When the same iodine products are given intravenously, in comparatively small daily doses, the course of the syphilitic infection is favorably influenced, as indicated by the more rapid disappearance of spirochetes and clearing up of lesions.

5.—In some instances, the intravenous administration of iodine compounds produces more rapid results than the oral, even with smaller doses.

6.—The three iodine compounds employed in our experiments failed to produce a complete cure in rabbit syphilis, regardless of the route of admininstration or the number and magnitude of the doses.

7.—The investigation establishes the fact that iodine compounds exert a definitely favorable influence upon experimental syphilis. However, they are mild antisyphilitic drugs and afford only symptomatic effects in spirochetal infections.

Sodium Thiosulphate

Sodium thiosulphate is a most efficacious agent in combating the toxic reactions resulting from the treatment of syphilis by heavy metals, especially the trivalent arsenic compounds of which the arsphenamines are representative. It is absolutely nontoxic, up to 2 Gm., when given intravenously.

It has most effect when given intravenously but is almost as effective when given by mouth. It may be given in large doses (1 Gm. to 1.75 Gm.), but the moderate doses (0.5 Gm. or 0.6 Gm.) is found more efficient.

Daily injections are usually given in the more severe reactions, such as exfoliative dermatitis or encephalitis; or biweekly injections in dermatitis and the milder jaundice reactions.

The combination of intravenous and oral medication is the method of choice and produces more satisfactory results. The daily ingestion of large amounts of fluids is recommended while this therapy is being used.—Dr. L. G. Beinhauer, in *Am. J. Syphilis*, Jan., 1928.

Tryparsamide and Neurosyphilis

In *Illinois* M. J., for September, 1927, Dr. G. W. Schelm, of the U. S. Veterans' Bureau, discusses his results from the use of tryparsamide and mercury in 100 cases of neurosyphilis.

The author has found tryparsamide to have properties which render it especially desirable in neurosyphilis. It first came into extensive use in 1923, since which time the data were collected for this series of cases. Tryparsamide has not been found to be of especial benefit in primary and secondary syphilis. The drug does not have an irritating action upon the tissues and can be injected subcutaneously or intramuscularly.

The following technic has been used in the administration of tryparsamide: the drug as prepared at present comes in 3-gram, sterile glass ampoules. The setup requires the following articles:

First: 2 medicine glasses
10-cc. Luer syringes
Hypodermic needles, 19 to 22 caliber (length 1½")
1—250-cc. Erlenmeyer flask, with freshly triple distilled water.

Second: 4 sterile hand towels; gauze sponges, q.s.; cotton pledgets or cotton applicators.
Tr. iodine or 70% alcohol.
12" rubber tubing, ¼" diameter, for tourniquet.
1 shallow pan to hold sterile goods and instruments.

The above instruments are all sterilized and placed between two sterile towels. The sterile medicine glasses are placed on a sterile towel, one is filled with freshly distilled water (triple distilled); into the other the contents of the ampoule, namely, the tryparsamide, is added. One or more doses may be prepared at once if the work is being done in institutions or clinics where more than one is being treated at a time. For each dose of tryparsamide, 10 cc. of water are drawn into the Luer syringe (before fixing the needle) and this forcibly emptied into the glass containing the drug, after which the syringe is used in mixing the drug and drawing it up and expelling it from the syringe. It is only necessary to repeat this a few times, the drug being very soluble. Finally, 10 cc. of the solution are drawn into the syringe, the needle fixed, and the contents injected into the arm, the tourniquet being released after the vein has been entered. Seventy-percent alcohol or a weak solution of tincture of iodine is applied to the skin at the proposed site of the entrance of the needle. The median basilic or adjacent veins are used, because of convenience.

When a series of cases is treated, a separate syringe is used for each case, to expedite matters. During the entire procedure, strict attention is paid to asepsis.

Mercury salicylate was given in 1-grain doses, intramuscularly, into the buttocks. A suspension was prepared so that each cc. of this oil (olive oil 75%, lanolin 25%) contains 1 grain of mercury salicylate. This suspension is self-sterile.

The tryparsamide was given in courses of 8 injections each, supplemented by mercury salicylate, grains 1, intramuscularly. Each of these was given weekly, separated by several days.

Tryparsamide and mercury, used in combination, had a beneficial effect, physically and mentally, in over 50 percent of the 100 cases of neurosyphilis treated.

The physical, mental and serologic conditions tended to run a parallel course in response to the treatment. Occasionally, however, the serology would be rendered normal, while the physical and mental conditions remained unchanged, and vice versa. This undoubtedly could be attributed to the anatomic location or the pathologic changes produced in the nervous system as the result of the disease.

Upon the laboratory findings the influence of these drugs was also decidedly favorable, as shown in the case of the spinal fluids, where the cell count was first to show a diminution; second, in over 20 percent of the cases, the Wassermann test was rendered negative—those that were negative at the beginning of treatment remained so, while many were reduced in the intensity of the reaction; third, the globulin was reduced in intensity of the reaction in a large percentage of cases, but few were rendered negative. The Lange gold chloride test was the last to show the effect of the treatment. In this series 20 percent of the curves were rendered normal; in other cases the curve remained stationary or manifested an improvement, only a few showing reverse changes. The blood Wassermann test was rendered negative in one-third of the cases in this series, which is higher than other writers using this treatment have found.

No cures can be claimed for any in this series, despite the fact that some entered into an excellent state of remission; rather, the disease appeared to be arrested. The treatment prolongs life; it improves or eliminates many of the undesirable and troublesome symptoms and conditions, thus making the patient's life more endurable and occasionally restoring him to a useful social position. The drugs have a more favorable action upon early cases of neurosyphilis who are in a fair physical and mental condition. Far advanced and terminal cases show no decided improvement.

Two or more courses of treatment were necessary before any decided beneficial results were obtained. The improvement was usually first noted in the physical condition. Mentally they improved more slowly and often not so completely as in the physical state. Certain of the serologic tests often showed changes after one course of treatment, while others did not show the effects until several courses had been administered.

Several doses of neoarsphenamine given during the rest period appeared to act as an adjuvant to the tryparsamide and mercury treatments.

The writer stresses that careful attention should be given to the personal hygiene and general physical condition of the patient during and following the antiluetic treatment.

Availability of Calcium in Calcium Lactate

According to F. W. Heyl and M. C. Hart, in *J. Am. Pharm. Assn.*, March, 1928, when calcium lactate is superimposed for 10 days upon an acidotic, calcium-deficient, but vitamine-containing diet, a quantity amounting to approximately 9.5 Gm. (147 grains) is required to establish calcium equilibrium. Compared with milk this represents 2.5 or more times as much calcium as is necessary when using the latter.

The authors' experiments showed that the urinary calcium excretion was markedly increased, about 10 percent of the calcium increment taking this route. The same tendency is noted in using milk.

The urinary phosphorus excretion was decreased and phosphorus retention secured by the ingestion of calcium lactate. In this diet, the original Ca:P ratio was 2:9; and the favorable influence upon phosphorus metabolism may be due to the establishment of a more favorable balance of 14:9. However, in the cases of milk experiments, a ratio of 5:9 yielded a more decided phosphorus retention.

Mercurochrome

The relative rates of healing of focal infections in guinea pigs trated by mercurochrome, locally or by injections, has been studied experimentally by Drs. J. E. Sanner and J. H. Hill, of Baltimore. Their findings, published in *Surg. Gynec. Obst.*, April, 1928, are as follows:

1.—Guinea pigs with induced abdominal abscesses, treated locally, as compared with untreated controls, showed a prompt and rapid drop in the wound counts, with healing before the controls.

2.—The animals treated intraperitoneally also showed a rapid drop in counts and healing more rapid than in the animals treated locally.

3.—The intravenous injection of 5 milligrams per kilo of body weight also caused a prompt and rapid drop in the count, in some cases quicker than in the animals treated locally.

Digitalis Preparations Intravenously

Dr. Harold E. B. Pardee, of New York, has done some interesting work on digitalis preparations, which he reports in *J.A.M.A.*, July 21, 1928.

He finds that the liquid preparations available in ampules, for parenteral administration, are no more potent in effect than corresponding quantities of tincture of digitalis, given by mouth, but that they act more rapidly when injected.

He is further of the opinion that the doses ordinarily given are too small too produce the desired effects, and recommends that one minim of Digalen, Digifolin solution or Digitan Solution, be injected for each pound of body weight; or 1/100 grain (0.6 mgm.) of Digitalin tablets, amorphous (Burroughs, Wellcome & Co.) to each 18 pounds of body weight. It is better for the physician who fears such doses to give 1/4 minim per pound and repeat every 45 minutes for 4 doses, constantly watching for toxic symptoms. If necessary, the doses may then be continued every 3 or 4 hours, up to 8 doses, *but no more.*

The intravenous injections produce most prompt and powerful results, in an emergency; intramuscular injections are somewhat slower, especially when the circulation is abnormal; and the delay is even greater after hypodermic injections.

Ephedrine in Spinal Anesthesia

Dr. H. L. Wehrbein, of the Urological Service of Bellevue Hospital, N. Y., in *Brit. J. Anesthesia*, April, 1928, says that spinal anesthesia has become the most frequently employed method of anesthesia in their urologic work, but that the alarming drop in blood-pressure which often occurs is a drawback. Since trying ephedrine as a stimulant it has solved the problem to a large extent.

During one year they have used ephedrine in over 300 cases of spinal anesthesia. At first it was used prophylactically in all cases of low blood-pressure. But it was found that there was no safe minimum and it is now the adopted policy to give 50 mgm. of ephedrine, subcutaneously, in all cases, five minutes before the spinal anesthesia is begun. They also tried a few times to counteract an alarming blood-pressure drop after spinal anesthesia by intravenous injection of ephedrine. This was strikingly succcessful.

The average drop in blood-pressure after spinal anesthesia is 10 to 30 mm. within 15 minutes; the average drop in 30 consecutive medicated cases was nil.

Ephedrine is an efficient drug for the maintenance of blood pressure during spinal anesthesia.

Acriflavine in Encephalitis

There are different types of epidemic encephalitis—the lethargic, the myoclonic and the maniacal.

According to Dr. W. D. Patton, in *Canad. M.A.J.*, April, 1927, it is possible that the disease is a septicemia or bacteremia due to the influenza organism, and on the basis of this belief the author started intravenous therapy in 1924. Ten cases have been treated, 1 of the lethargic, 4 of the myoclonic and 5 of the maniacal type.

Dr. Patton considers acriflavine the most valuable agent for intravenous therapy. The results in the cases in which it was tried were so prompt and so apparent that he hopes others will try this drug to confirm or refute its merits.

Treatment was begun in the acute stage with 10 cc. of 0.5 percent solution of neutral acriflavine in physiologic saline solution. Daily doses were given until 25 cc. were reached. Usually good results were manifest after the fourth dose and continued until recovery.

Three cases similarly treated by colleagues of Dr. Patton have given equally satisfactory results, both in lethargic and other types of epidemic encephalitis. No reactions or untoward results have been observed.

The acriflavine should always be freshly prepared, dissolved in isotonic saline solution, boiled and cooled to body temperature, given preferably by means of a syringe with a fine needle, and *injected slowly*.

Acriflavine in Gonorrhea

Dr. M. L. Boyd, in *J. Urol.*, Jan., 1928, reports that acriflavine, in a 1:1,000 aqueous solution, has unfailingly and almost immediately stopped acute gonorrheal urethritis in 40 cases treated by him. In all cases the treatment was begun while the infection was limited to the outer part of the pendulous urethra. No other medication has, in his hands, given such excellent results.

Two injections of acriflavine are made daily, one in the morning and one in the late afternoon; no other medication is used during the first week unless the patient is given some mild urinary sedative.

The injection is held in with pressure exerted by forefinger and thumb on the urethra back of the glans. The penis is then wrapped in cotton, held upright for from 10 to 15 minutes, and the acriflavine then allowed to ooze out.

The Salicylates and Magnesium in Rheumatism

In an article in *Ann. Intern. Med.*, July, 1928, by Dr. Harlow Brooks, of New York, on the treatment of rheumatism, he says, in regard to the salicylates, that they tremendously allay the sufferings of the patient, and that they add to his comfort, probably more than all our other therapeutic factors put together.

Magnesium salts, combined with the various salicylates, seem to act as they do with morphine, by intensifying the effects and making smaller dosage adequate, and, at the same time, reducing intolerance. Recent experimental work has shown that this combination reduces the toxicity of the salicylates and that magnesium augments the antipyretic action of sodium salicylate and aspirin.

Dr. Brooks says that it seems probable that some similar action may explain the apparent greater therapeutic effect of the salicylates when given in association with magnesium in cases of rheumatism.

Gold Compounds in Medicine

In studying the various gold compounds, which have been developed within the past ten years and which are used in medicine, one is impressed by the outstanding fact that the number of gold compounds containing sulphur exceed those which do not contain sulphur. There is a certain affinity of gold for sulphur.

The number of gold compounds that have therapeutic value and which contain sulphur is undoubtedly greater than the sulphur-free combinations. Chemists and chemotherapeutists working along these lines therefore seem to be led by the idea of selecting compounds containing sulphur in which gold is then introduced, because a real organic gold compound—a carbon-gold linking—has heretofore not been known. This problem has recently been solved but it remains to be seen whether the carbon-gold linking offers any therapeutic advantage over the gold-sulphur linking. — DR. F. R. GREENBAUM, in *Med. Rev. of Rev.*, Jan., 1928.

Ammonium O-Iodoxy Benzoate in Arthritis

Dr. Millard Smith, of Ann Arbor, Mich, in *New Eng. J. Med.*, July 19, 1928, gives a resume of his results from the treatment of arthritis with ammonium o-iodoxy benzoate during the past 2 years. Of 65 patients, who had received at least five intravenous injections of the drug, 24 were markedly improved and 12 partially relieved. Those who were not relieved were afflicted with constipation of long standing but no focus of infection could be found. Such patients are probably absorbing toxins from their gastrointestinal tracts.

No patient in whom the only focus of infection was found in the teeth, tonsils, nose or sinuses failed to obtain marked improvement from the drug.

Dr. Smith thinks that, in the case of patients weighting less than 100 pounds, the initial dose should not be more than 0.3 Gm., nor subsequent doses larger than 0.7 Gm. Patients above this weight may be started on 0.5 Gm. and usually tolerate 1.0 Gm. subsequently.

Auxiliary physical therapy measures are strongly favored.

Postural Hypotension with Syncope, Treated with Ephedrine

In a small number of apparently healthy persons, the assumption of the upright posture produces sufficient fall in blood pressure to cause marked dizziness and syncope. This condition is known as postural hypotension and, according to Drs. D. G. Ghrist and G. E. Brown, of the Mayo Clinic, in *Am. J. Med. Sc.*, March, 1928, only a few cases have been recorded. Two cases have been observed in the Clinic.

The essential disturbance in this disease is the lack of resistance in the splanchnic vessels to shifts in the blood mass and absent or diminished vagus regulation of the heart rate to changes in the blood pressure.

The successful treatment by ephedrine, in one of the cases observed at the Mayo Clinic, allows hope that this drug exercises a specific alleviative effect on the disease, by stimulating the myoneural structures of the vasomotor nerves.

NEW BOOKS

Marriott: Chemistry in Medical Practice

RECENT ADVANCES IN CHEMISTRY IN RELATION TO MEDICAL PRACTICE. *By W. McKim Marriott, B.S., M.D., Dean and Professor of Pediatrics, Washington University School of Medicine; Physician-in-Chief, St. Louis Children's Hospital. Lectures of the San Diego Academy of Medicine, Series of 1927. Illustrated. St. Louis: The C. V. Mosby Company. 1928. Price $2.50.*

The large place which laboratory procedures occupy in present-day clinical medicine, as well as the advanced knowledge which has been acquired regarding the significance of chemical actions in the body in health and disease, make it almost imperative that the clinician should have at least a working knowledge of chemistry, especially biologic chemistry.

Dr. Marriott's book is designed to fulfill this purpose. It consists of six lectures in which are comprised: fundamental chemical consideration; acidosis and alkalosis; the chemistry of the blood; foods and metabolism; and the endocrines.

In these lectures the busy practitioner will not only find a large amount of information of the greatest practical importance to him, but he has the newest facts presented in a manner that does not call for any particular technical knowledge of chemical methods in order to understand them. The material has been written from the point of view of the clinician.

Hazen: Syphilis

SYPHILIS. *A Treatise on Etiology, Pathology, Symptomatology, Diagnosis, Prognosis, Prophylaxis, and Treatment. By Henry H. Hazen, A.M., M.D., Professor of Dermatology and Syphilology, Medical Department of Georgetown University; Professor of Dermatology and Syphilology, Medical Department of Howard University; etc. Second Edition. Illustrated. St. Louis: C. V. Mosby Company. 1928. Price $10.00.*

The first edition of Dr. Hazen's treatise on syphilis appeared in 1919, the book containing several chapters contributed by collaborators.

The present edition may be classified as a clear and succinct exposition of the present-day clinical aspects of syphilis. There are 24 chapters written by Dr. Hazen and collaborators and the exhibitions of syphilitic lesions, with their consequences in the various regions and organs, are dealt with in a natural and consecutive manner. There is little ground for conjecture and theorizing, as the etiologic, pathologic and therapeutic aspects of syphilis are now so well known that a textbook almost becomes descriptive only.

The chapter on syphilis of the central nervous system, which the author has entirely rewritten, is especially illuminating and thoroughly up-to-date. The short chapter on syphilis of the endocrine glands will also bring new facts to many.

Much of the present edition has been rewritten, owing to the many developments in syphilology within recent years, and where revision only was called for this has been done. The book is well illustrated, the pictures not being merely for ornament, but exponents of matters to which the author calls special attention.

Dr. Hazen's book may be confidently recommended to physicians who want a concise textbook covering syphilis in the light of present-day advances and which boils down the vast literature of the subject.

Crane & Patterson: Literature of Chemistry

A GUIDE TO THE LITERATURE OF CHEMISTRY. *By E. J. Crane, Editor of Chemical Abstracts and Austin M. Patterson, Professor of Chemistry, Antioch College, Formerly Editor of Chemical Abstracts. New York: John Wiley & Sons, Inc. 1927. Price $5.00.*

The eight chapters of instruction in literature "searching", followed by a "Bibliography of Articles Related to Chemical Literature", with its list of libraries, journals and books ought to prove to be valuable as a reference work for the student and research worker in the chemical field.

The authors, experienced abstractors, have concentrated much information into little space.

C. F. L.

Annual Medical Report of the United Fruit Company

SIXTEENTH ANNUAL REPORT, 1927. *Medical Department, United Fruit Company, Boston, Mass. Gratis on request.*

The Annual Report of the Medical Department of the United Fruit Company is always very interesting reading.

The Company maintains a number of well-equipped and up-to-date hospitals throughout Central America and there are generally some valuable reports in regard to tropical diseases from the staffs of those hospitals. Many of the papers in the present report deal with the control and treatment of malaria. The success of the measures adopted for checking mos-

quito-breeding and for the destruction of mosquitos should be a matter of interest to those engaged in mosquito warfare.

One of the most important phases of the Company's medical work is its research for the discovery of antivenins. Snake bite has been responsible for such a number of deaths in the past that is was imperative to seek remedies and, to a great extent, this research work has been highly successful.

As these reports are presented free, physicians who are vitally interested in large cooperative medical projects of the kind herein referred to should try to obtain copies.

Abderhalden: Biologic Methods

HANDBUCH DER BIOLOGISCHEN ARBEITSMETHODEN. *Geh. Med.-Rat Prof. Dr. Emil Abderhalden, Direktor des Physiologischen Institutes der Universitat Halle a.d. Saale. Abt. V, Methoden zum Studium der Funktionen der einzelnen Organe des tierischen Organismus. Teil 5A, Heft 4 und Teil 8, Heft 2. Berlin & Wien: Urban & Schwarzenberg. 1928. Price Mk.8.—(each).*

Subsection 4 of Section 5A, Part 5, of the above handbook deals with the methods of testing muscle and nerve physiology, and contains five articles by different specialists.

Subsection 2 of Section 8 of Part 5 deals with the circulatory and respiratory apparatus and contains four articles, including one by Henderson and Murray, of Cambridge, Mass.

Boyd: Preventive Medicine

PREVENTIVE MEDICINE. *By Mark F. Boyd, M.D., M.S., C.P.H., Member of Regular Field Staff, International Health Division of the Rockefeller Foundation; formerly Professor of Bacteriology and Preventive Medicine in the Medical Department of the University of Texas. Third Edition Revised. Philadelphia and London: W. B. Saunders Company. 1928. Price* $4.50.

In a general way it may be said that the broad tendency in the practice of medicine during recent years is to adopt the methods of preventive medicine to individual hygiene. Apart from the infectious diseases, there is an effort, fostered by public education, to forestall disease by rigid attention to obviating the causes.

In the matter of preventive medicine, on the whole, there has been too great an aloofness on the part of the medical profession. This applied not only to public health but to personal hygiene. Dr. Boyd rightly remarks that, if this neglect continues, the opportunities, which are now within the grasp of medical practitioners, will lessen and the field will be taken away from them by a changing public sentiment. It therefore behooves physicians, if they wish to retain prestige and public leadership in their communities, to be fully familiar with the principles of preventive medicine, both public and individual.

Dr. Boyd's book, which is now in its third edition, is necessarily concise, covering as it does the whole field of preventive medicine. While it contains nothing essentially new or surprising, it includes all that is necessary to make anyone with intelligence familiar with all the modern methods of fighting disease. A book of this kind, up-to-date, should be on every doctor's bookshelf and should be thoroughly studied.

Aulde: Calcium Therapy

CALCIUM THERAPY. The Fundamental Principle Underlying Rational Therapeutics. *By John Aulde, M.D., Formerly Assistant Physician, Out-Patient Department, Jefferson Medical College Hospital; Demonstrator of Physical Diagnosis and Clinical Medicine, Medico-Chirurgical College; etc. Philadelphia, 1024 Walnut St.: John Aulde, M.D. 1928. Price* $5.00.

That calcium deficiency—or rather the failure of proper assimilation of calcium—in the organism is the cause of many systemic disorders there appears to be but little doubt.

Dr. Aulde has been engaged in studies of calcium therapy for the past fifteen years and the present book represents mostly a collection of the various publications on the subject which he has made in that time. So far as we can follow the author's views, most of the disease conditions referred to are considered as the result of disordered mineral balance in the body, an excess especially of deleterious magnesium and a deficiency of calcium.

There seems undoubtedly to be a strong foundation in fact for many of the author's opinions, especially the efficacy of colloidal calcium administration in heart and blood conditions, but his observations are presented in such a heterogeneous jumble and in such a disconnected way that it seems to be impossible to follow them in any kind of a sequential manner.

There apparently is much good material in the contents of this book, but the task of discovering it would be like picking needles from bundles of hay, and probably most physicians would find such a task tedious.

Terry and Pellens: The Opium Problem

THE OPIUM PROBLEM. *By Charles E. Terry, M.D., and Mildred Pellens. For The Committee on Drug Addictions in collaboration with The Bureau of Social Hygiene, Inc. New York, 61 Broadway: Committee on Drug Addictions. 1928. Price* $5.00.

The use of opium and its derivatives in therapeutics, as well as the frequency with which cases of drug addiction are met, make every physician interested in the opium question.

The book under review is a digest of information collected by the Committee on Drug Addictions—a group of University men, physicians and social workers—in collaboration with the Bureau of Social Hygiene, New York, this information being gathered from literature and other sources in an attempt to obtain a thorough grasp of the extent of chronic opium addiction in the United States, its causes, the nature of its effects and the factors concerned with its control.

The voluminous matter collected by the Committee has been digested and condensed into the present book of over 1,000 pages. It pre-

sents a wide divergence of opinion on the various aspects of opium addiction, as both a medical and social problem. It has been published because the Committee believed that it would be advisable to inform the public, so far as possible, regarding actual conditions in opium traffic and use, so as to create a healthy and well informed public opinion before the Committee proceeded to take steps in combating the manifest evils arising from opium misuse.

The matter is one which should be of particular concern to physicians, as leaders of public opinion on such questions of social hygiene in their immediate neighborhoods. To them the feeling of the Committee in publishing the book applies with special force, namely: "To acquaint those potentially or actually interested with some idea of the different phases of the problem and of various theories which so far have been elaborated and to suggest, through its reviews of existing records, other and broader fields for study and research."

Fuhrmann: Chemistry of Foods and Condiments

DIE CHEMIE DER NAHRUNGS- UND GENUSSMITTEL. *Ein Lehrbuch für Chemiker und Mediziner. Von Prof. Dr. Franz Fuhrmann, Vorstand der Lehrkanzel für technische Mykologie und Chemie der Nahrungs- und Genussmittel der Technischen Hochschule in Graz. Mit 42 Abbildungen im Text. Berlin and Wien: Urban & Schwarzenberg. 1927. Price, geh. Mk. 24.-, geb. Mk. 27.-*

Dr. Fuhrmann's textbook bears all the earmarks of very extensive study and knowledge of all matters connected with the chemistry of digestion and of food stuffs within the body.

The book will be of great value as an elaborate technical treatise for special students, but is scarcely one that would be of direct practical benefit to physicians.

Clendening: Modern Treatment

MODERN METHODS OF TREATMENT. *By Logan Clendening, M. D., Associate Professor of Medicine, Lecturer on Therapeutics, Medical Department of the University of Kansas; etc. With Chapters on Special Subjects by Several Other Authors. Second Edition. St. Louis: The C. V. Mosby Company. 1928. Price $10.00.*

When the first edition of this book was published, in 1924, the author stated that its purpose was to present a comprehensive statement of the best modern thought and practice upon the treatment of diseases included in the general specialty of internal medicine. One reason for writing it was that the author, as a practical teacher, found most textbooks on the subject of therapeutics did not fit his ideas as to what such a book should be.

The text is divided into two parts: Part I—general therapeutics—gives the general methods used in internal practice—drugs, physical therapy, hydrotherapy, etc.; Part 2—special therapeutics—gives the application of therapeutics to particular diseases.

In the first part the chapters on drugs and dietetics are especially good. In the second part, the treatment of diseases of metabolism and of the digestive system appear to demand special mention.

In bringing out a second edition, advantage has been taken to include all real advances in therapeutic methods, such as liver diet in pernicious enemia, scarlet fever antitoxin, parathyroid feeding, the use of ephedrine and other new drugs, malarial treatment of neurosyphilis, etc. Several of the special articles have been written by recognized authorities.

There is a good index and many illustrations are used.

General practitioners who are looking for a single volume covering modern methods of treating internal diseases in a comprehensive manner will find that this fulfils the object admirably.

Graham, et Al.: Diseases of the Gall-Bladder

DISEASES OF THE GALL-BLADDER AND BILE DUCTS. *A Book for Practitioners and Students. By Evarts Ambrose Graham, A.B., M.D., Professor of Surgery; Warren Henry Cole, B.S., M.D., Instructor in Surgery; Glover H. Copher, A.B., M.D., Assistant Professor of Surgery; and Sherwood Moore, M.D., Professor of Radiology; all of Washington University School of Medicine, St. Louis. Illustrated with 224 Engravings and 8 Colored Plates. Philadelphia: Lea & Febiger. 1928. Price $8.00.*

We are only beginning to appreciate the important part which gall-bladder disorders may play in generalized ills. Thanks to the brilliant work of Graham and his associates, there are now available reliable methods for visualization of the gall-bladder and a study of its functioning.

Although the first important paper in this new development of cholecystography appeared as recently as 1924, a considerable literature has developed, making a volume covering the field much to be desired. Not only do the authors of this book ably summarize this literature, but they add timely comments based upon their own wide experience.

The first portion deals with the anatomy of the normal and abnormal biliary systems, including the much-discussed mechanism of gall-bladder emptying. Cholecystitis and biliary calculi are the subjects of succeeding chapters, following which we find an extended discussion of the symptoms and clinical diagnosis of diseases of the gall-bladder.

The succeeding 100 pages are devoted to radiology of the biliary tract. Particular emphasis is placed upon cholecystography by means of tetraiodophenolphthalein and its isomer phenoltetraiodophthalein. Intravenous administration is favored by the authors, but ample evidence is presented to show the almost equal value of oral administration, as practiced by most physicians.

Inasmuch as a good roentgenogram is worthless without intelligent interpretation, this phase receives careful consideration. In this connection it is of interest that the visualization of stones—the object of workers prior to 1920—is a comparatively uncommon occurrence by present methods, diagnosis being based primarily upon proper filling and emptying. Quite remarkable diagnostic efficiency has been attained;

of 446 gall-bladders reported as pathologic by various authors, 97.5 percent were found to be diseased on operation. Normal shadows do not, however, indicate as certainly a normal organ, for but 74 percent of 115 such diagnoses were substantiated on surgical examination.

Chapters 8 and 9 are devoted respectively to tests of hepatic function and the surgical treatment of cholecystitis.

Today a gastrointestinal examination can not be considered as complete without accompanying cholecystography. This volume by Graham and his associates makes available in excellent form the information desired by all interested in this field.

D. L. T.

Cameron: Biochemistry

A Textbook of Biochemistry. *For Students of Medicine and Science. By A. T. Cameron, M.A., D.Sc., (Edin.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; etc. With a Foreword by Professor Swale Vincent, LL.D., M.D., D.Sc., F.R.S.E., F.R.S.C., Professor of Physiology, University of London. With 2 Plates and 12 Text Figures. New York: The Macmillan Company.* 1928. *Price* $5.50.

Dr. Cameron's textbook is based on his practical experience in teaching biochemistry to medical students.

The book is essentially an elementary one and presupposes a knowledge of organic and physical chemistry sufficient to elucidate the procedures pursued in biochemical investigations.

The work may be recommended because it is written by a teaching chemist, fully familiar with the perplexities which ordinarily beset students in this subject. It will also be found of benefit to practicing physicians who make their own laboratory investigations, or even to laboratory technicians.

Medical Education

Proceedings of the Annual Congress on Medical Education, Medical Licensure and Hospitals. *Chicago: The American Medical Association, 535 No. Dearborn St.,* 1928.

The annual appearance of this volume is eagerly awaited by all who are sincerely interested in medical education and is of great value as a presentation of the most modern thought and practice along this line.

The publishers will furnish full particulars on application.

Van Der Leeuw: Conquest of Illusion

The Conquest of Illusion. *By J. J. Van der Leeuw, LL.D., author of "The Fire of Creation", "Gods in Exile", etc. New York and London: Alfred A. Knopf.* 1928. *Price* $3.50.

Beginning with the thesis that philosophy is the quest of life, the author sets out to show where that quest may lead us; and, with the further statement of Plato, that philosophy is the birth of wonder, he challenges us to satisfy our wonder by daring explorations.

Science is the study of the phenomenal world, which is not and never can be, *the* world, but is, for each of us, merely the *impression* which the unknown reality makes upon our consciousness—our own special and particular *world-image*. Science studies and explains the *how* of the manifestated universe.

Philosophy, on the other hand, is concerned with ultimate truth—the inner realities of *things in themselves* and the *why* of the tremendous operations which take place within us.

What we perceive as a tree may, for aught we know, be a mathematical point, possessing such qualities that it makes, *on our consciousness*, an *impression* which causes us to say, "There is a tree." We, thereupon, *project* that image in our consciousness externally and believe that we are seeing an actual reproduction of the thing in itself. So long as we believe and act as though our particular world-image were ultimate reality, we are bound by illusion; but when, perceiving the image, we realize its illusory, character, we are free.

"The mystery of life", says Van der Leeuw, "is not a problem to be solved; it is a reality to be experienced." He also maintains that, while the intellect is sufficient for the purposes of science, we must make use of the intuition (or knowledge by direct experience) to develop a sound philosophy. Our *interpretations* of reality may change, but not Reality itself.

The chapter headings of this delightful volume give a hint of the fascinating paths along which the author leads us: The Quest of Life; From the Unreal to the Real; Intuition and Intellect; Absolute and Relative; The Mystery of Creation; Spirit and Matter; The Phantom of Evil; Freedom of Will; Justice of Life; The Immorality of the Soul; In the Light of the Eternal These cannot however, convey an impression of the sparkling simplicity and directness of the philosophical presentation.

Since reading Ouspensky's "Tertium Organum" we have encountered no book so exciting and satisfying as this one.

To the materialistic scientist it will be rank heresy; to the causal reader, "highbrow nonsense"; but to those with a bent for philosophy it will prove an undiluted joy and a powerful stimulant.

International Clinics

International Clinics. *A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles by Leading Members of the Medical Profession Throughout the World. Edited by Henry W. Cattell, A.M., M.D., Philadelphia, with the collaboration of several others. Volume II. Thirty-eighth Series,* 1928. *Philadelphia and London: J. B. Lippincott Company. Price* $3.00 *per volume;* $12.00 *per year.*

This is the 150th quarto-anniversary volume of this well-known serial and is an exceptionally fine one. The five opening papers are reminiscences and reviews of medical progress during the period since the inception of the *International Clinics*.

In the diagnostic section there is an excellent paper by Dr. Brickner, of New York, on ruptures of muscles and tendons and one by Dr. Longaker, of Philadelphia, on cervicitis.

In the section on medicine, Dr. Seale Harris, of Birmingham, Ala., contributes two papers on

pernicious anemia, and in the surgical section Dr. F. H. Albee, of New York, gives a clinic on arthrodesis, fractures, bone grafts, etc.

The other sections contain several excellent clinical papers, many of them by foreign authors.

Haggard: Health and Disease

WHAT YOU SHOULD KNOW ABOUT HEALTH AND DISEASE. *By Howard W. Haggard, Associate Professor of Applied Physiology, Yale University. With an Introduction by Yandell Henderson. Illustrated. New York and London: Harper & Brothers.* 1928. *Price* $5.00.

The author has presented the main facts of health and disease so far as they rest upon a scientific foundation. The presentation is, and to a great extent must necessarily be, from an almost purely physiologic standpoint. The book is similar to others of the same kind which have been written for the educated layman.

In his introduction to the book, Professor Henderson says, "The broad, general, major matters in the science of modern medicine are of no greater volume and of rather less difficulty than those of such subjects as physics or economics." Several reasons might be advanced in opposition to this view—for instance, medicine has to a large extent a metaphysical basis and we have scarcely yet reached the stage when we can reduce epilepsy and psychoses to foot-pounds.

Professor Henderson's attempt to inject an aspect of materialistic philosophy into the book seems unnecessary, and we think it should have been allowed to stand on its own merits as a record of more or less established facts.

The book has little of value to the practicing physician, but it is one that he may recommend to intelligent patients and laymen that "want to know."

Sanger: Woman

WOMAN AND THE NEW RACE. *By Margaret Sanger. With a Preface by Havelock Ellis. New York: Eugenics Publishing Company.* 1923. *Price* $2.00.

Of the people who write upon the control of human reproduction, there are few who can speak with more authority than does Margaret Sanger —and she speaks in no uncertain voice. Other people may talk mildly of the advantages of contraception: She declares that the woman who bears a large family is *immoral*—a sinner against herself, her children, her husband and the nation.

She states (and backs her argument up with cogent logic) that unemployment, destitution, war, famine and pestilence are not so much "acts of God" as acts of too-prolific mothers. And she reasons that, since women are responsible, in the last analysis, for these evils, it is women who must pay the debt to the race and to the Country by remaking the world, through intelligently controlled motherhood.

The history of woman's revolt against enslavement by the State, the Church, and by individual men is traced with sufficient detail, and startling statistics regarding present economic and social conditions are quoted from unimpeachable sources.

She maintains that limited fertility is not for the poor and undesirable citizens alone, but that if women of the wealthy and cultured classes were to have large families that fact would defeat its own ends.

The book is a plea to women to free themselves from the traditional tyranny of past centuries, by upholding their right to bear children only when they choose to do so. It is an impassioned plea, and as such it may be a bit hyperbolic in spots, but the cause is a worthy one and, in the main, the statements are reasonable and the conclusions soundly drawn.

While addressed to women particularly, this volume should be read by everyone who is interested in social problems, especially by physicians, who will have much to do with the coming of the new order of things which Mrs. Sanger forecasts.

Cohn: Peripheral Paralysis

DIE PERIPHERISCHEN LÄHMUNGEN. *Diagnostik, Untersuchungstechnik. Prognostik und Therapie. Von Prof. Dr. Toby Cohn, Berlin. Mit 64 Abbildungen im Text. Berlin and Wien: Urban & Schwarzenberg.* 1927. *Price, geh.* Mk. 18.-; *geb.* Mk. 21.-

Dr. Cohn's book is an extension of his article on the diagnostic technic in peripheral nerve paralyses in Kraus and Brugsch's book on special pathology and treatment. The subject is covered very thoroughly.

Hollós: Tuberculous Intoxications

TUBERCULOUS INTOXICATIONS. *Concealed and Masked Tuberculosis. A Clinical Study. By Joseph Hollós, M.D., Pathologist of St. Vincent's Hospital, Staten Island, New York. Edinburgh: E. & S. Livingstone, 16 and 17 Teviot Place. New York: William Wood & Co., 156 Fifth Ave.* 1928. *Price* $3.25.

Every physician is constantly coming into contact with cases of manifest tuberculosis, pulmonary and other. But there are many cases in which this widespread disease is masked under aspects which simulate other disease entities. Indeed, Dr. Hollós considers that, in the majority of cases, tuberculosis does not present itself in its manifest customary forms but remains concealed and has the appearance of anemia, neurasthenia, etc. This book is devoted to the description of these various concealed and latent forms of tuberculosis.

The present work is an enlargement of a similar book published in French by the author in 1910.

There is a good deal of matter of an original kind which will be of much interest to physicians who are directly concerned with the tuberculosis problem, especially diagnosis; and perusal of this little volume will throw light on a great many conditions which puzzle the general practitioner. In the author's view, tuberculosis, like syphilis, has many insidious and devious methods of manifesting itself within the body.

MEDICAL NEWS

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Dr. Lowsley to Conduct Clinic in England

Dr. Oswald S. Lowsley, consulting urologist of several New York hospitals, director of the James Buchanan Brady Foundation, of the New York Hospital, and author of a textbook on urology and other works, has been invited to speak on the prostate gland before the Royal Society of Medicine, England and to conduct a prostate clinic at St. Paul's Hospital, London.

Dr. Lowsley is a graduate of Stanford and Johns Hopkins Universities and was a Lieutenant in the Medical Department of the Naval Reserve Corps during the War.

Important Meetings This Autumn

The meeting of the American College of Physical Therapy, at the Stevens Hotel, Chicago, October 8 to 13, 1928, has been announced, as has also that of the Interstate Postgraduate Medical Association, in Atlanta, Ga., October 15 to 19. Do not overlook these important meetings.

The **Southern Medical Association** will meet in Asheville, North Carolina, November 11 to 14, 1928. This is always an important meeting, with fine, practical programs. Write to C. P. Loranz, Empire Bldg., Birmingham, Ala., for full particulars, and *plan to go.*

Civil Service Examinations

The United States Civil Service Commission announces the following examinations:

Associate Statistician (Public Health), $3,200 a year.

Assistant Statistician (Public Health), $2,600 a year.

Applications received until Oct. 19, 1928.

Physiotherapy Aide
Physiotherapy Pupil Aide

Applications received until Nov. 27, 1928.

Full information may be obtained from the United States Civil Service Commission, Washington, D. C., or from the secretary of the United States Civil Service Board of Examiners at the post office or customhouse of any city.

Alumni Meeting

The Ensworth - Central - Northwestern Medical College Alumni Association will hold its annual meeting and dinner, following the clinical conference in Kansas City, in St. Joseph, Mo., Oct. 11, 1928. Send names to Dr. Chas. W. Fassett, Secty., 115 East 31st St., Kansas City, Mo.

Send For This Literature

To assist doctors in obtaining current literature published by manufacturers of equipment, pharmaceuticals, physicians' supplies, foods, etc., CLINICAL MEDICINE AND SURGERY, North Chicago, Ill., will gladly forward requests for such catalogues, booklets, reprints, etc., as are listed from month to month in this department. Some of the material now available in printed form is shown below, each piece being given a key number. For convenience in ordering, our readers may use these numbers and simply send requests to this magazine. Our aim is to recommend only current literature which meets the standards of this paper as to reliability and adaptability for physicians' use.

Both the literature listed below and the service are free. In addition to this, we will gladly furnish such other information as you may desire regarding additional equipment or medical supplies. Make use of this department.

J- 1 Helping the Cell to Help Itself, 32-page booklet by The Alkalol Co.

J- 2 Your Prestige and Profit. 8-page booklet. The Carroll Dunham Smith Pharmacal Co.

J- 3 Storm Binder and Abdominal Supporter, 4-page folder by Dr. Katherine L. Storm.

J- 4 Pluto Water. Its Medicinal Values. 16-page booklet. French Lick Springs Hotel Co.

J- 5 Ethical Medicinal Specialties. 8-page booklet. A. H. Robins Co.

J- 6 The Journal of Organotherapy. 95-page booklet published monthly. G. W. Carnrick Company.

J- 7 The Cure of Cystitis, Pyelitis and other Inflammatory Conditions of the Urinary Tract. Chicago Pharmacal Co.

J- 9 Hang This Up—It Tells How to Make Percentage Solutions. Sharp and Dohme.

J- 14 The New Ultra-Violet Therapy. McIntosh Electrical Corporation.

J- 17 An Index of Treatment. Burnham Soluble Iodine Co.

J- 20 A Survey of Focal Infection. Fellows Medical Co.

J- 37 pH 7.4, Alka-Zane. Wm. R. Warner & Co., Ltd.

J- 38 Hycol. The Certified Disinfectant. Merck & Co.

J- 39 A Convincing Solution of an old Problem, Isacen. The Hoffmann-La Roche Chemical Works.

J- 40 Truth Spreads by Testimony, Isacen. The Hoffmann-La Roche Chemical Works.

J- 41 The Specific Treatment of Pneumonia with Numoquin-Base. Merck & Company.

J- 45 Vera-Perles of Sandelwood Comp. Paul Plessner Co.

J- 46 Bedtime Nourishment. Mellin's Food Company.

J- 47 Campho-Phenique in Major and Minor Surgery. Campho-Phenique Company.

J- 49 The Calcreose Detail Man. Maltbie Chemical Co.

J- 50 Outwitting Constipation. Standard Oil Co.

J- 51 The Ideal Anti-Gonorrheic. Riedel & Co., Inc.

J- 52 Cre-So-Mul. First Texas Chemical Mfg. Co.

J- 56 Regaining Health. How Science Can Guide You! The Fleischmann Company.

J- 58 The Pharmacology of Cod Liver Oil. Smith, Kline & French Co.

J- 67 The Electro-Pathology of Local Inflammation. The Dionol Company.

J- 70 Yeast Therapy. The Fleischmann Company.

J- 78 Nourishment for Adults and Children in Health or Illness. Mellin's Food Co.

J- 82 Service Suggestions, September-October, 1928. Victor X-Ray Corp.

J- 84 Latent Constipation—A Diagnostic Problem, Agarol. Wm. R. Warner & Co.

J- 85 Ultraviolet for Health. Hanovia Chem. & Mfg. Co.

J- 87 Journal of Intravenous Therapy. Loeser Laboratory.

J- 93 Britesun Therapeutic Booklet. Britesun, Inc.

J- 94 A Compendium of Glandular Therapy. Colwell Pharmacal Corporation.

J- 95 Everything for the Sick—Lindsay Laboratories.

J-103 The Electron, September, 1928. McIntosh Electrical Corporation.

J-106 Acidosis as a Complication in Winter Diseases. William R. Warner & Co.

J-110 When Colds Hang on and Coughs are Stubborn. The Hoffmann-La Roche Chemical Works.

J-112 Atophan after more than Fifteen Years of ever expanding use, etc. Schering & Glatz.

J-113 Forcep Deliveries and Versions. Battle & Co.

J-114 Infra Red Therapy. Britesun, Inc.

J-116 Hemo-Glycogen, The New Product of Hemoglobin Compound and Liver Extract. Chappel Bros., Inc.

J-120 Building Resistance. William R. Warner & Co., Ltd.

J-122 Cardiazol, an Emergency Stimulant and Sustaining agent for the heart. E. Bilhuber, Inc.

J-127 The Surgical Treatment of Goiter. The C. V. Mosby Co.

J-128 A New Book Written in Simple Language, Getting Well and Staying Well. (Tuberculosis). The C. V. Mosby Company.

J-135 Enemata—Petrolagar. Deshell Laboratories, Inc.

J-136 Obesity in Females. The Tilden Company.

J-139 How to Save Children from Goiter. Morton Salt Company.

J-153 Caprokol. Sharp & Dohme.

J-156 Siomine (Methenamine Tetraiodide). Pitman-Moore Company.

J-167 A New Animal Skin Hormone Preparation. Armorskin Corporation.

J-169 The Quartz Lamp, Sept. 15, 1928. Hanovia Chemical & Mfg. Co.

J-170 Making Vitamin D Plentiful and Palatable. Pitman-Moore Company.

J-176 The Hormone, September—24 pages and cover, published bimonthly. The Harrower Laboratory.

J-180 The Treatment of Malignant Tumors of the Pharynx and Larynx by Diathermy. Victor X-Ray Corporation.

J-181 Diathermy in Pneumonia and Its Sequelae. Victor X-Ray Corp.

J-182 The Treatment of Tumors of the Bladder by Means of Surgical Diathermy. Victor X-Ray Corporation.

J-183 Prevention of Reactions Following Intravenous Injection of Dextrose. Loeser Laboratory.

J-184 Drosine, a National Product, Antiseptic Deodorant. The National Drug Co.

J-185 Ephedra (Ma Huang) Physiologic and Therapeutic Report. The National Drug Co.

J-186 Detoxification in the Treatment of Infection. Wm. S. Merrell & Co.

J-187 Electro-Surgery. Victor X-Ray Corporation.

J-188 Medical Pocket Quarterly, Sept., 1928, Vol. 9, No. 2. Reed and Carnrick.

J-189 High Blood Pressure — Treatment with Theocalcin. E. Bilhuber, Inc.

J-190 Symptosium on the Intravenous Administration of Dextrose (d-glucose). Loeser Laboratory.

J-191 Studies on Edible Gelatine in the Dietary. Chas. B. Knox Gelatine Co., Inc.

J-192 A New Way to Treat Hyperacidity. The Wander Co.

J-193 Bulletin which Describes the Many Advantages of the New Solar Arc Lamp. Sanitarium & Hospital Equipment Co.

J-194 Fracture Book—1928 Edition. DePuy Mfg. Co.

J-195 Booklet on Lacto-Dextrin. Battle Creek Food Co.

J-196 "Facts Worth Knowing". Intravenous Products Co. of America, Inc.

J-197 Bulletin. Illinois Post Graduate Medical School, Inc.

J-198 Book and Portfolio of Letters in Evidence. Philo Burt Co.

J-199 Activin in Non Specific Protein Therapy. Ernst Bischoff Co.